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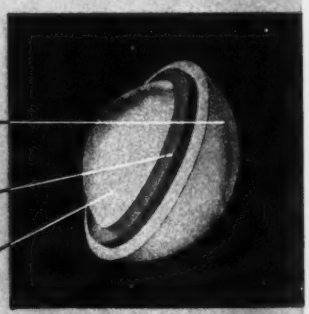

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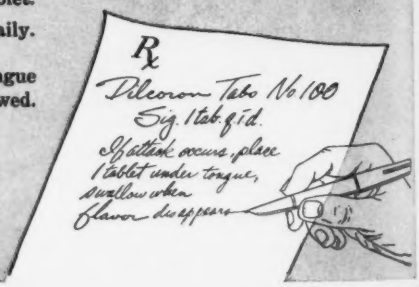

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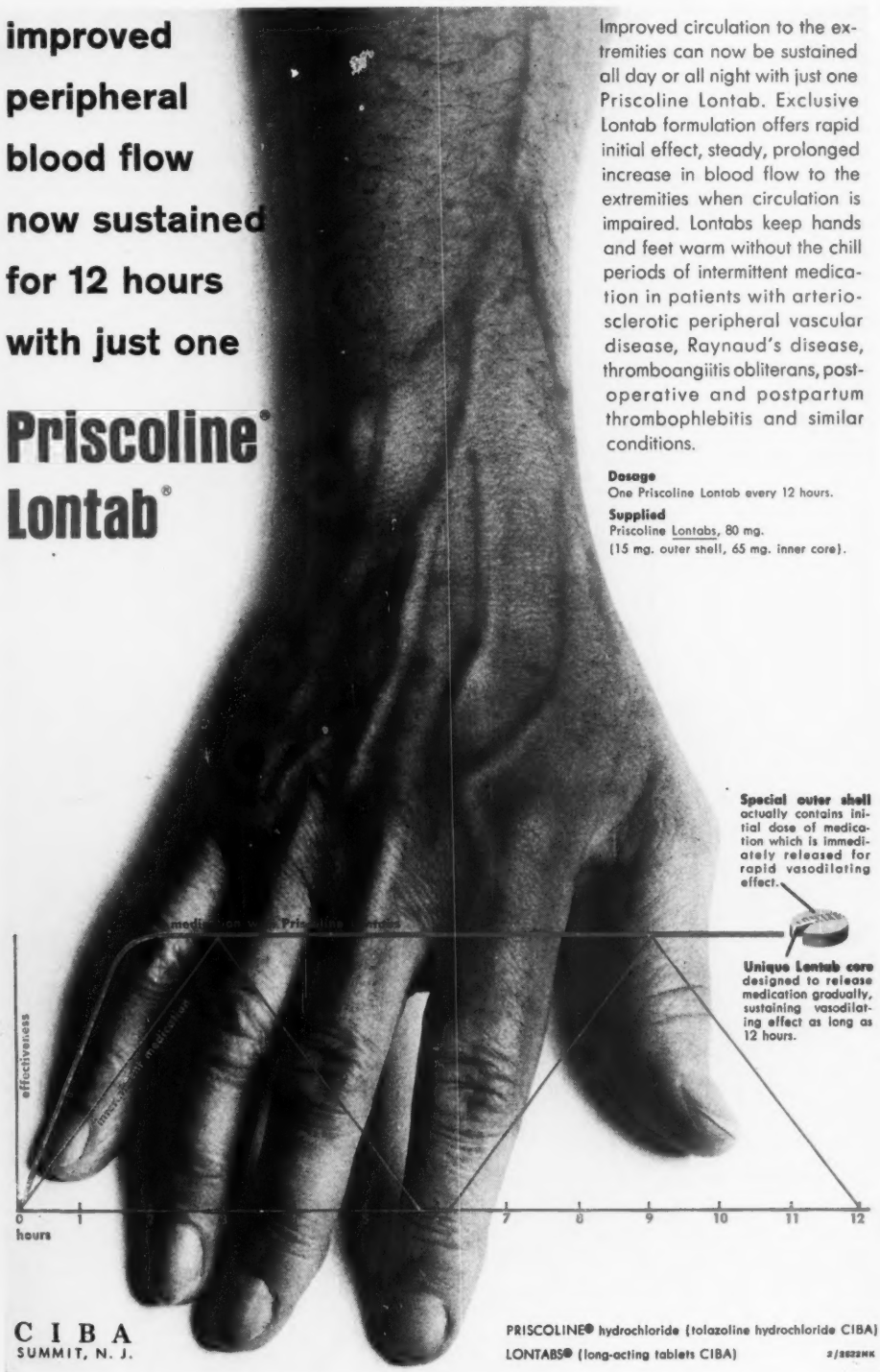

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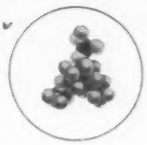

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Editorial

The Role of Vessel Tone in Pulmonary Hypertension

KNOWLEDGE of the mechanism by which pulmonary hypertension occurs and is maintained is still rudimentary. The recent increased interest in this topic is due to both scientific curiosity and the practical necessity of predicting those patients in whom the pressure in the pulmonary artery might be expected to decrease after closure of a congenital cardiac defect and those in whom it will persist or increase.

Pressure is a function of flow and resistance; in this case, the latter is the resistance to flow offered by the pulmonary vascular bed. The difficulty lies in accurately measuring this resistance and in deciding from the resulting values whether they represent changes in vessel caliber. Usually, the pressure gradient across the pulmonary vascular bed (mean pulmonary arterial pressure minus mean left atrial pressure) is measured, and this value is divided by the mean blood flow in order to obtain a value for the pressure-flow ratio, which is considered to be a measure of resistance to blood flow. The mean pressure gradient across the pulmonary vascular bed in resting healthy persons is usually less than 10 mm. Hg. Determination of this gradient requires measurement of at least two pressures, which are associated with uncertainties of zero reference points, variations in the level of intrathoracic pressure and other factors that render an absolute error of at least several millimeters of mercury likely. In the presence of severe pulmonary hypertension, these absolute errors are relatively small in contrast to the normal situation, in which the absolute magnitude of the error in measurement is such as to allow detection of only relatively large percentage changes in pulmonary vascular resistance. For instance, a 50 per cent decrease in resistance in a normal resting person, if all other factors remained constant, would be associated with a decrease in the pressure gradient of approximately 5 mm. The large relative error in measurement of such a small change in pressure is evident. However, if the pressure gradient is in the range of 50 to 100 mm., as occurs in pulmonary hypertension, the relative error in such measurements decreases to acceptable levels.

In any event, the value for the pressure-flow ratio that is obtained must be interpreted with caution, since the pulmonary vascular bed is a complex system with fluctuating pressure and flow. Furthermore, changes in the frequency and amplitude of these fluctuations are common owing to alterations in cardiac rate and stroke volume. Interpretation of the physiologic significance of these measurements is complicated further by changes in intrathoracic pressure of variable frequency and amplitude associated with the respiratory cycle and by the possibility of alterations in resistance to air flow, all of which factors may affect the pressure-flow ratio across the pulmonary vascular bed without active changes in the caliber of the pulmonary vessels.

Studies on animals, in which many of these factors can be accurately controlled, have es-

From the Mayo Clinic, Rochester, Minn.

tablished clearly that the pulmonary vessels are capable of active changes in caliber. They can be constricted by a variety of agents, of which 5-hydroxytryptamine (serotonin) is the most potent.[1] De Burgh Daly[2] has demonstrated both vasoconstrictor and vasodilator fibers whose stimulation results in active change in the caliber of these vessels. More recently, Daly and Daly[3] noted that carotid chemoreceptor stimulation causes a reflex decrease in pulmonary vascular resistance mediated by vagal cholinergic fibers. The mechanism of the increase in pulmonary arterial pressure in animals, which often occurs during hypoxia, is still the subject of much controversy. Recent work by Duke[4] indicates that the increase in pressure is caused mainly by constriction of pulmonary vessels via a direct effect of the lowered oxygen tension on the smooth-muscle fibers.

It would be advantageous if one could determine accurately the major site of changes in resistance, that is, whether it is precapillary, capillary or postcapillary. Gilbert and associates[5] recently studied the resistance in arterial and venous segments in isolated dog lung perfused at a constant flow. They recorded changes in lung weight continuously with measurements of pressures in the pulmonary artery, at the pulmonary arterial wedge, in small pulmonary veins and in the left atrium. Their studies showed that bacterial endotoxin causes constriction of pulmonary veins, that histamine constricts both arteries and veins, and that 5-hydroxytryptamine causes chiefly precapillary constriction. In the intact animal or man, in whom changes in lung weight cannot be determined simultaneously, the inability to measure accurately the pressure in pulmonary capillaries limits attempts to define the exact site of increased resistance.

A catheter impacted in a branch of the pulmonary artery obstructs the flow to the segment of lung supplied by the artery in question. This, therefore, becomes essentially a static system in which the pressure is essentially that of the left atrium, and the pulmonary vasculature in this segment can be considered as an extension of the catheter to the left atrium. However, since these measurements are made under conditions of obstructed blood flow to this segment of the lung, it should be remembered that the pressures obtained may bear little relationship to the pressures actually existing in the pulmonary capillaries or veins of this particular segment of the lungs when blood is flowing in this system. This is particularly true in the presence of pulmonary venous obstruction, since the pulmonary arterial wedge pressure measured under such circumstances depends on how effectively the blood flow is stopped in the segment of lung in question. If flow is absent, the wedge pressure obtained will be equivalent to the left atrial pressure. If flow continues, the wedge pressure usually will be greater than the left atrial pressure but almost certainly less than the "in vivo" pulmonary venous pressure, since the wedged catheter has reduced, but to an unknown degree, the blood flow through this vein. The "in vivo" pulmonary capillary, pulmonary venous and left atrial pressures in such a situation may bear little relationship to the recorded wedge pressure. However, it is probably true to say that, in man, a "wedged" catheter under most conditions measures the left atrial pressure with acceptable accuracy, and, when combined with simultaneous measurement of pulmonary arterial pressure, permits changes in pressure gradient across the pulmonary vascular bed as a whole to be assessed.

Recent experiments have demonstrated that the normal pulmonary vessels in man need not behave wholly as a passive viscoelastic system. Fritts and co-workers[6] have demonstrated the presence of tone in these vessels, and recent observations by Patel and associates[7] have shown that they are capable of constricting when norepinephrine is used.

Increased resistance to flow across the pulmonary vascular bed, presumably in the precapillary vessels, often occurs in the pulmonary hypertension associated with acquired or congenital heart disease. More muscle is present in these vessels, and, therefore, the

potential is present for greater changes in vessel caliber. That active changes in caliber can occur has been demonstrated by Paul Wood and his colleagues[8] in patients with mitral stenosis, in whom acetylcholine decreases the pulmonary vascular resistance. Valvotomy also decreases the resistance, whereas exercise in such patients may augment it. Smooth-muscle tone also plays a part in the pulmonary hypertension associated with congenital heart disease. Burchell and co-workers[9] demonstrated that breathing mixtures low in oxygen often increases the resistance, while breathing oxygen often decreases it. Harris[10] was the first to demonstrate a decrease in pulmonary arterial pressure after rapid injection of acetylcholine into this vessel in some patients with congenital heart disease. With continuous infusion of acetylcholine into the pulmonary artery, a decrease in resistance often is obtained; when the infusion of acetylcholine is combined with breathing oxygen, an even greater reduction in resistance occurs.[11] This reduction is apparently independent of the initial level of the pulmonary arterial pressure and the type of lesion, regardless of whether it is an atrial or ventricular septal defect, an aortic-pulmonary communication or a patent ductus arteriosus. The decreased resistance results from the opening up of vessels somewhere in the lung, although it cannot be said whether it is caused by the opening up of vessels previously closed or by dilatation of existing vessels. Some patients do not respond even to a combination of these two stimuli and presumably have what Edwards[12] has defined as the "high-resistance and low-reserve" type of pulmonary vascular bed. In practice, one would like to be able to produce a maximal release of tone in these vessels in order to measure the resistance caused by the histopathologic changes in the vessels themselves. That the increase in pulmonary vascular resistance in these patients is solely precapillary is a matter of inference from the absence of clinical evidence of pulmonary capillary congestion and from the site of the smooth-muscle hypertrophy and the associated pathologic changes. One cannot say whether the tone is normal or excessive in degree, as the advent of increased muscle in the vessel wall alters its viscoelastic properties and mechanically may cause changes in resistance. There may be more muscle with normal tone or more muscle with excessive tone.

Obstruction to pulmonary venous drainage, as in mitral stenosis or as may be found in cor triatriatum or in some cases of total anomalous pulmonary venous connection, often is associated with increased resistance to flow through the pulmonary vessels, despite the fact that the mechanical effects of such an obstruction would tend to increase the caliber of the vessels and decrease the resistance. Ferencz and Dammann[13] demonstrated that pulmonary venous obstruction in patients with congenital heart disease is associated with arterial narrowing. Thus, the increase in pressure resulting from the obstruction may initiate and maintain tone in the precapillary vessels. A similar explanation can be applied in mitral stenosis, in which reduction in pressure by valvotomy causes relaxation of vessels by reducing vascular tone and in which an increase in pressure during exercise may result in constriction.

In patients with interventricular communications, a defect greater in area than 1 cm.^{2}/M.^{2} of body surface offers so little resistance to flow across it that the pressure is equalized in the two ventricles. The hemodynamics are similar in patent ductus arteriosus; the short wide ductus, like the large ventricular septal defect, constitutes a nonobstructive opening, permitting free communication between the pulmonary and systemic vessels, so that the pressures in the aorta and the pulmonary artery are equivalent. The amount of blood that enters the pulmonary circulation as compared to that in the systemic circulation is thus a function of the relative resistance of these two circuits. The fetal type of vessel persists in such patients both in the small arterioles (Civin and Edwards[14]) and in the major pulmonary arteries (Heath and Edwards[15]). In this situation, both increased pressure and flow can act on the pulmonary

vessels and may constitute a stimulus for the persistence of the smooth muscle and for the maintenance of its tone. This situation also may be accompanied by an increase in left atrial, and hence pulmonary venous, pressure caused by a variable degree of left ventricular failure. The left atrial pressure is reduced after surgical closure of the patent ductus or the ventricular septal defect. Therefore, increased pulmonary venous pressure may be an etiologic factor in the increased pulmonary vascular resistance. On the other hand, Scebat and associates suggested that the stimulus for the muscle tone arises not in the lung but in the systemic tissues so that, as the oxygen needs of the tissue increase, there is a reflex decrease in systemic resistance and an increase in pulmonary resistance. However, there is no convincing evidence from experiments with autonomic-blocking agents that the autonomic nervous system plays a role in pulmonary hypertension. Whatever the final theory, it also must explain the observations of Dammann and Ferencz that the resistance in patients with large ventricular septal defects first tends to decrease toward normal in the early postnatal months.

In patients with atrial septal defects who have a progressive increase in resistance to flow through the pulmonary vessels, the tone of the vessels contributes to the resistance, as inhalation of oxygen and injection of acetylcholine can dilate the vessels. In idiopathic pulmonary hypertension, although the resistance appears to be fixed when the condition is advanced, acetylcholine can cause dilatation of the pulmonary vessels in the early stages, with a pronounced decrease in pulmonary arterial pressure. Again, one can only speculate on a possible mechanism or mechanisms by which the tone is maintained. Suffice it to say that tone in pulmonary vessels now has been demonstrated in every abnormality in which pulmonary hypertension occurs, but that the manner in which this tone is maintained is still unknown.

From the practical point of view, the demonstration that oxygen or acetylcholine or both are capable of dilating the vessels in patients with pulmonary hypertension and congenital heart disease is no guarantee that closure of the defect will remove the stimulus that controls the smooth-muscle tone and thus permit relaxation to occur. Greater understanding of the factors involved in maintaining and producing pulmonary hypertension and in altering the caliber of pulmonary vessels in both health and disease still lies in the future.

JOHN T. SHEPHERD
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Pre-Harveian Doubts of Galenic Doctrine

Although it was long believed that the discovery of the circulation of the blood had its inception in Europe in the middle decades of the sixteenth century, about a quarter century ago it was learned that an earlier description of the pulmonary transit of the blood had been written in the thirteenth century by a Moslem physician, Ibn Nafis. The discovery either in the orient or the occident presumes a prior dissatisfaction with the reigning Galenic doctrine, and it seems likely that the first attack upon this well-established doctrine would have been an oral one. Thereafter, at least in the case of Europe, there was published, as we know, a certain amount of pioneer research into isolated factors which was ultimately brought together to form the description of the new doctrine of the lesser circulation or pulmonary transit of the blood. While it is unlikely that we shall ever know the oral doubts expressed in Europe, we can, however, trace a certain amount of the preliminary work published, some of which must certainly have implied doubt, that of Berengario da Carpi, Niccolo Massa, Andreas Vesalius, Giambattista Canano, and oddly enough, even of that arch-Galenist Jacobus Sylvius, leading to the relatively complete descriptions of Servetus, Valverde, and Colombo.

There has long been some question as to whether or not the prior work of Ibn Nafis had become known in Europe and contributed to the discovery there. Thus far, however, no relationship has been found between his Commentary on Avicenna, which contains the description of the lesser circulation, and western medical thought in the sixteenth century. Nevertheless, in a work entitled "Sixth consideration on the pulse taken from the Arabic book of Siraxus," published in Venice in 1547, are imbedded some interesting and suggestive, but not conclusive, statements drawn from an unidentified work of Ibn Nafis translated by Andrea Alpago. These statements represent problems which oppose the Galenic doctrine, as it was related to the heart and arterial system, and orthodox answers which seek to reconcile such doubts or contradictions. It appears as if the problems and their answers were a kind of academic exercise allowing Ibn Nafis to express doubts which he held and yet by his answers, unsatisfactory as they might be, to remain within the Galenic camp. Hence it is suggested that these statements are drawn from an early work prior to his final description of the pulmonary transit of the blood and therefore his open break with Galen. Indeed, even in this treatise Ibn Nafis is referred to as speaking on occasion "in disproof of the opinion of Galen."—Charles D. O'Malley. *A Latin Translation of Ibn Nafis (1547) Related to the Problem of the Circulation of the Blood.* History of Medicine and Allied Sciences **12**: 248, 1957.

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Maintenance of Cardiorespiratory Functions by Extracorporeal Circulation

By JOHN H. GIBBON, JR., M.D.

I AM GREATLY honored to have been selected to give the Lewis A. Conner Lecture before this association. I propose to discuss in this lecture some of the unsolved problems that have arisen from the use of extracorporeal blood circuits, a field in which I have long been interested. Twenty-four years ago at the Massachusetts General Hospital, we constructed an artificial heart-lung apparatus that was capable of maintaining the cardiorespiratory functions of cats for more than 4 hours with the pulmonary artery completely occluded.[1] A few years later, continuing this work at the Harrison Department of Surgical Research at the University of Pennsylvania, we were able to carry the entire cardiorespiratory functions of cats for as long as 26 minutes with prolonged healthy survival of the animals.[2] World War II interrupted our work in this field, but it was resumed at the conclusion of the war. Six years were then spent in further experimental work in animals, with increasingly long periods of total bypass of the heart and lungs with survival,[3-5] a decreasing mortality rate, and successful experiments in which atrial[6] and ventricular[7] septal defects were created and closed. There followed on May 6, 1953, the first successful open-heart operation on a human being in which the entire cardiorespiratory functions were maintained by an extracorporeal circulation.[8] The heart and lungs were bypassed for 26 minutes while a large atrial septal defect was closed with sutures under direct vision. The patient, an 18-year-old girl, is now, 5 years later, healthy and leading a normal life. Today, as every member of this audience knows, surgical operations on the interior of the heart under direct vision, while the cardiorespiratory functions are maintained by an extracorporeal circulation, are commonplace in many medical centers in this country and abroad. While the mortality in the correction of the simple congenital or acquired cardiac defects now approaches that of other operations of similar magnitude in the hands of experienced surgical teams, much additional knowledge is required to increase the safety of the procedure, especially in the more complicated cases.

This lecture concerns the multitude of physiologic problems that have arisen from the use of a mechanical apparatus to take over temporarily the functions of the heart and lungs. Much virgin territory remains for the competent investigator to explore and conquer.

BLOOD FLOW AND PRESSURE DURING EXTRACORPOREAL CIRCULATION

Very little accurate data exist on cardiac output during operations under general anesthesia.[9] The flow of blood through the extracorporeal circulation, however, can be easily and accurately measured. There is abundant evidence that low flow rates, 25 to 35 ml. per Kg. body weight per minute, produce harmful effects upon the organs and tissues of the body.[10-14] It is now generally agreed that flow rates in the neighborhood of 2.3 L. per M^2 per minute, or higher, are desirable.[15] There is also considerable evidence that the rate of blood flow should be greater in infants and young children than in adults.[16]

Initial Fall in Mean Pressure

The fall in mean blood pressure, which is not infrequently seen on the initiation of total bypass, is generally assumed to be the result

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of a blood flow through the extracorporeal circuit that is less than the cardiac output of the patient immediately preceding total bypass. The addition of blood to the combined system of the subject's vessels and the extracorporeal circuit is frequently resorted to in order to increase the blood flow and to raise the subject's blood pressure. Yet if the presumption is correct that the observed fall in blood pressure on initiating total bypass results from a blood flow through the circuit less than the preexisting cardiac output of the subject, it is clear that attention must be directed towards overcoming the technical factors that may contribute to this diminished blood flow. An example of such a technical factor is the decreased internal cross-sectional area of the cannulae in the venae cavae, as compared with the internal cross-sectional area of the cavae themselves. Obviously the nearer these cross-sectional areas approach one another, the easier it will be to obtain the same venous blood flow, and thus the same arterial blood flow and cardiac output, as existed before. Another technical factor that may limit blood flow through the circuit is the resistance offered by the cannula returning the blood to the subject's arterial system. There is a limit to the pressure which can be employed to overcome this resistance because of (to mention only one facet) the hemolysis resulting from the passage of blood from a high pressure area to a low pressure area through a narrow orifice.[17]

If, on the other hand, the above-mentioned presumption is inaccurate, and the flow of blood through the extracorporeal circuit is as great, or greater than that which existed immediately prior to initiation of total bypass, then the fall in blood pressure must be related to a decrease in peripheral resistance. Under these circumstances, adding blood to the circuit would compensate for the blood pooled in the area of vascular relaxation. In this case, vasodepressor substances in the blood in the extracorporeal circuit should be sought and if possible eliminated. Other factors, of course, may be responsible for the vasodilatation, such as reflexes arising from baroreceptors in the walls of the atrial,[18] the venae cavae, or pulmonary vessels.

Volume of Blood in the Lungs

On the initiation of complete cardiopulmonary bypass, theoretically the volume of blood in the lungs should be markedly reduced, thus increasing the blood volume in the combined system of extracorporeal circuit and the subject's vascular system. This additional volume should counteract to some extent vascular pooling in the subject's body, if this is the basis of the observed fall in blood pressure. In the acyanotic patient, the foregoing remarks should be true. On the other hand, in the cyanotic patient who already has a large bronchial artery component entering the pulmonary capillaries, the cessation of blood flow through the pulmonary arterial tree should tend to reduce the resistance in the pulmonary capillaries and to increase the blood flow into the left side of the heart from the bronchial arteries through the pulmonary capillaries and veins. Experience with open-heart operations in the laboratory and in human patients has shown the importance of providing an escape for this blood from the left side of the heart when cardiac arrest is employed.[19–21] Accurate data on the blood volume and blood flow through the lungs should be obtained before, during, and after bypass, in order to provide for the greatest safety of the patient during the operation.

Reversal of Flow in Aorta

In much of the early experimental work on animals, the arterialized blood from the extracorporeal circuit was returned to the subject's arterial system by way of a centrally directed cannula in a femoral artery. In much of the early human operative work, this blood was returned through a centrally directed cannula in the left subclavian artery. In the last few years, however, most surgeons have employed the femoral artery for return of this blood as in the early animal experiments. This shift was made because of the technical difficulty in exposing the left subclavian artery through the usual transverse thoracotomy incision, the inaccessibility of the artery from a

median sternotomy, and also because it shortened the time during which the thorax was open. While many of the aortic branches, i.e., innominate, left carotid, left subclavian, intercostals, and renal arteries, leave the aorta almost at right angles, the mesenteric arteries form an obtuse angle with the normal direction of blood flow. Due to piezometric effects, it is possible that the flow of blood through the mesenteric arteries and celiac axis may be considerably reduced when the direction of blood flow is reversed in the aorta by employing a centrally directed cannula in the femoral artery to return the arterialized blood. If the femoral artery continues to be employed for this purpose, the flow through the superior mesenteric artery as well as the other great branches of the aorta should be measured before and after reversal of the blood flow. The development of an accurate electromagnetic blood flow recorder[22] provides a suitable technical device for obtaining this much-needed information. Dr. John Templeton of our department has recently abandoned the femoral artery, and now returns the arterialized blood through a cannula inserted into the ascending aorta through a stab wound. This method eliminates reversal of flow through the aorta, permits the employment of a cannula with a larger internal lumen than the femoral artery, obviates the possibility of impairment of the blood supply to a lower extremity, and is technically simpler and more rapid than femoral artery cannulation.

Relation of Oxygen Consumption to Blood Flow

Many recent reports have shown that, within limits, the oxygen consumption of the body during extracorporeal bypass of the heart and lungs is directly related to blood flow.[11, 13] A blood flow significantly below basal levels is associated with decreased oxygen consumption. This decrease in oxygen consumption results in a metabolic acidosis that progressively increases in severity throughout the period of low blood flow. Therefore, in human patients maintained at normal, or only slightly reduced body temperature, it is highly desirable to maintain rates of blood flow high enough to avoid tissue hypoxia. Certainly the postoperative period is hazardous enough without imposing the additional burden of metabolic acidosis.

Mean Aortic Blood Pressure During Bypass

In the mammalian vascular system, because of variable peripheral resistance, blood flow and blood pressure will not always vary in the same direction or to the same extent. Recent experimental work with extracorporeal circulations has shown that renal function becomes impaired as the mean aortic pressure declines, and ceases at mean pressures below 50 mm. Hg.[11] Thus, not only should the blood flow be kept at nearly normal basal levels to avoid tissue hypoxia, but also the blood pressure should be kept at a mean level of 80 mm. Hg, or above, in order to ensure normal function of the kidneys and of other bodily organs and tissues. Further work in this area, particularly regarding hepatic function,[12] is required.

Tension of Gases in Blood

Excessive Oxygen Tension

Pendido et al.[23] have shown that with a bubble-type oxygenator, the tension of oxygen in the blood may reach or exceed 700 mm. Hg. There is, of course, no advantage to oxygen tensions of this magnitude in blood of normal hemoglobin content, as the hemoglobin will be normally saturated with oxygen at a tension in the neighborhood of 100 mm. Hg. Theoretically, there might be a slight advantage to oxygen tensions approaching 700 mm. Hg during extracorporeal bypass if the blood flow were inadequate. Every 100 ml. of blood under these circumstances would then carry 2.1 ml. of oxygen in physical solution in the plasma in addition to the 20 ml. carried in the form of oxyhemoglobin, whereas normally with 100 mm. Hg oxygen tension, only 0.3 ml. of oxygen is carried in the plasma of each 100 ml. of blood. This approximately 10 per cent increase in oxygen-carrying capacity per unit of blood theoretically could compensate

for a 10 per cent decrease in the rate of blood flow to the tissues. On the other hand, high tensions of oxygen in the blood introduce the hazard of oxygen emboli in the vascular system if the patient's body temperature is above the temperature of the blood as it leaves the artificial oxygenator.

Oxygen poisoning from the prolonged inhalation of 100 per cent oxygen is well documented in both animals and man.[24] A tension of oxygen in the neighborhood of 700 mm. Hg for 1 hour is not toxic in man,[25] and no ill effects have been noted in dogs during cardiopulmonary bypass for 45 to 60 minutes with oxygen tensions of 600 mm. Hg in the arterial blood.[26] It will obviously not be easy to obtain accurate data on this matter because of the difficulty of controlling other parameters during the period of perfusion. Measurements of myocardial oxygen tension, by the methods which have been so admirably developed by Montgomery,[27] have already been reported during hypotension.[28] Studies during cardiac bypass should provide much useful data in this field.

Carbon Dioxide Tension before, during, and after Bypass

Some surgeons have recommended hyperventilation prior to bypass in order to reduce the carbon dioxide tension below normal.[29] This has been particularly advocated during the use of hypothermia alone for open cardiotomy. However, Bigelow has shown a subsequent increase in metabolic acidosis in patients subjected to respiratory alkalosis during the induction of hypothermia,[31] and mild degrees of hypothermia are commonly used in association with extracorporeal circulations. Vigorous hyperventilation by the anesthesiologist rarely reduces the carbon dioxide tension below 20 mm. Hg. In conscious man, very little impairment of mental acuity has been demonstrated until the carbon dioxide tension of arterial blood is reduced below 25 mm. Hg.[32] Nevertheless, lowering of carbon dioxide tension is known to produce cerebral vasoconstriction, and elevation of carbon dioxide tension to produce cerebral vasodilatation. Creech,[33] however, in a recent report observed no increase in cerebral blood flow in animals on extracorporeal circulation when 5 per cent carbon dioxide and 95 per cent oxygen were substituted for 100 per cent oxygen in the extracorporeal lung. If these observations can be substantiated, there would appear to be no advantage in raising the carbon dioxide tension during extracorporeal circulation in order to increase cerebral blood flow.

Relation between Respiratory and Metabolic Acidosis

Holaday[34] has reported that respiratory acidosis tends to produce metabolic acidosis. Recent observations in our laboratory have not confirmed this.[35] Dogs rebreathing carbon dioxide for a period of 2 hours, but with a normal arterial oxygen saturation, exhibited a lowering of lactic acid in the blood. There was the expected marked elevation of lactic acid in the blood in another group of animals breathing diminished concentrations of oxygen, but with normal carbon dioxide tension.

We, and others, have adopted the practice, when using extracorporeal circulation in patients, of maintaining a carbon dioxide tension of about 40 mm. Hg prior to and during bypass. Under these circumstances, any fall in the pH of the blood at the termination of the extracorporeal circulation is indicative of metabolic acidosis. This, fortunately, is usually of a degree not greater than that seen following most operations of similar magnitude. Its occurrence is obviously due to some degree of tissue hypoxia. Measures directed toward the avoidance of such metabolic acidosis should, therefore, be concerned with maintenance of adequate blood flow and pressure and the carrying of a normal volume of oxygen per unit volume of blood during the extracorporeal bypass.

The Heart during and after Bypass

Induced Cardiac Arrest

Probably the most interesting development in open cardiac surgery since the initiation of extracorporeal circulation is the concept of elective cardiac arrest. Cessation of myo-

cardial contractions and elimination of cardiac venous blood from the operative field allows the intracardiac surgical procedure to be performed with greater dispatch and accuracy. Elective arrest was first suggested by Melrose,[36] who induced cardiac arrest in dogs by injecting a solution of potassium citrate into the ascending aorta proximal to an occlusive clamp after the establishment of extracorporeal circulation. Effler[37] was the first to induce arrest by this means in human patients. Lam[38] employed acetylcholine for the same purpose in patients. Potassium citrate has been used more generally than acetylcholine, probably because potassium salts produce more complete relaxation of the heart. When acetylcholine is used, it is more difficult to produce complete arrest and the operative manipulations occasionally initiate contractions that may prove troublesome to the surgeon. Combinations of potassium and magnesium salts and other substances have also been used to produce cardiac arrest.[39-41]

Another method of inducing cardiac arrest during extracorporeal circulation consists in merely cross-clamping the aorta distal to the coronary ostia. This "anoxic" arrest has been employed successfully in patients by a number of surgeons,[42] who prefer it to the use of potassium or acetylcholine. Some surgeons who formerly employed potassium arrest now use it rarely because of the increased incidence of heart block in patients with myocardial damage and coronary insufficiency[43] and because of the conviction that the heart does not function as well during the immediate postoperative period following such arrest. This conviction is widely held despite the demonstration that no deleterious effect upon the capacity of the heart to do work can be demonstrated following potassium citrate arrest.[44] Induced cardiac arrest is usually not employed for the simpler lesions, such as incomplete atrial septal defects and pure pulmonic stenosis. It is generally employed in patients with the tetralogy of Fallot or ventricular septal defects.

The whole problem needs further investigation and clarification. The proponents of "anoxic" arrest produced by merely cross-clamping the aorta, state that all cardiac arrest is anoxic. This is true because the metabolism of the myocardium continues even when it is not contracting. Nevertheless, there is a marked difference in the degree of hypoxia of the myocardium resulting from potassium or acetylcholine arrest which occurs promptly, and that produced in "anoxic" arrest which occurs more slowly with progressively weaker contractions of the hypoxic left ventricle. The question to be answered may be stated simply. Which method is least harmful to the heart as measured by the ability of the heart to contract at a normal rate, rhythm, and force following the period of arrest?

Cardiac Hypothermia

Induced cardiac arrest has given rise to many other physiologic problems. We do not know whether some of the observed cardiac arrhythmias in the postoperative period are due to some special sensitivity of the sinoatrial node, the artrioventricular node, or the bundle of His to hypoxia and the accumulation of acid metabolites. With the ascending aorta cross-clamped and no blood flowing through the coronary vessels, the temperature of the heart will eventually fall to the ambient room temperature. The rate at which this drop in temperature occurs should be measured. It would appear obvious that the temperature of the thick-walled ventricles, and particularly of the left ventricle, which is unopened and contains blood, should fall less rapidly than the thin-walled atria. The effect such temperature differences may have on the spread of the electrical excitation waves, or the coordinated muscular contraction of the entire organ, is unknown and merits investigation. If differential cooling should prove to be responsible for any of the cardiac difficulties in the postoperative period then the results of uniform perfusion of the organ with a cold fluid should be explored. The cold would then be uniform and the heart could be rapidly cooled and rapidly rewarmed. The local hypothermia during bypass could be of any desired degree and might increase the safe duration of arrest by decreasing metal-

olism and the production of acid metabolites. The fluid used to perfuse the coronary arteries might be cold blood with a sufficient concentration of potassium salt or acetylcholine to maintain the arrest, or it could consist of cold plasma to maintain anoxic arrest. Paradoxically Kaplan and Fisher,[45] working with hypothermic dogs, found better tolerance of the heart to caval occlusion when the pericardium was perfused with warm saline. Much remains to be explored in this field.

Postoperative Pulmonary Dysfunction

Rather unexpectedly, postoperative pulmonary dysfunction has probably contributed more than other complications to the morbidity of open cardiac operations with an extracorporeal circulation. The usual postoperative pulmonary difficulties, such as retention of tracheobronchial secretions, or inadequate depth of respiration, appear to be enhanced after operations employing an extracorporeal circulation. Over and above these common difficulties, there not infrequently occurs in the immediate postoperative period some impairment of the gas exchange function of the lungs. This pulmonary dysfunction is manifested by both hypoxemia and hypercapnia, and is apparently unrelated to left heart failure.

Bronchial Artery Component of Pulmonary Blood Flow

It seems reasonable to assume that this pulmonary dysfunction arises during the period of bypass from some change in the *milieu interieur* of the pulmonary capillaries, the alveolar membranes, or the lining of the bronchioles. During bypass with cessation of blood flow through the pulmonary artery, there continues to be a small circulation of blood through at least some of the pulmonary capillaries by way of the bronchial arteries. As mentioned earlier, this flow of blood probably increases, because of decreased pressure in the pulmonary capillaries, when the flow through the pulmonary artery ceases. In cyanotic patients, the blood flow through the bronchial arteries may reach huge proportions. In the acyanotic patient without a septal defect, and without cardiac arrest, a vent need not be provided for the blood entering the left heart, because this blood will be ejected into the aorta by the left ventricle which is being perfused with oxygenated blood. If cardiac arrest is employed under these circumstances, a vent should be supplied for the escape of blood from the left atrium to prevent a gradual rise in pulmonary venous and capillary pressure with resultant pulmonary edema. Of course, cardiac arrest is rarely employed in such patients.

In the acyanotic patient with an atrial septal defect, cardiac arrest is also rarely employed, and even if it were, there would be an adequate vent for the blood in the left atrium through the septal defect when the right atrium is open. In the usual case without cardiac arrest, the presence of blood in the left atrium helps to avoid air embolism, and after the defect is closed, there is no danger of increased venous pressure with a resultant pulmonary edema, as the left side of the heart is able to eject any blood which reaches it because it is being perfused with oxygenated blood.

In the acyanotic patient with a ventricular septal defect and a left-to-right shunt, cardiac arrest may or may not be employed. If cardiac arrest is not employed, there is no danger of increased pulmonary venous pressure either before or after closure of the defect. If cardiac arrest is induced in these patients, a vent for the escape of blood from the left side of the heart should be provided after the defect is closed, unless the aortic clamp is promptly removed and vigorous cardiac contractions begin at once.

In the cyanotic patient with a septal defect and pulmonic stenosis, cardiac arrest likewise may or may not be employed. In any case, the flow of blood into the left atrium contributed by the bronchial arteries can be expected to be quite large. In such cases, when cardiac arrest is employed, it is always advisable to provide a vent in the left side of the heart for the escape of blood after closure of the septal defect.

The vents in the left side of the heart can be provided by a catheter inserted in the left ventricle near the apex of the heart or, more

simply and easily, by a catheter inserted into the left atrium through the left atrial appendage. Blood draining from such a catheter is, of course, returned to the extracorporeal circuit. By providing such vents in the left side of the heart when they are indicated, pulmonary edema from elevated pulmonary capillary pressure can be avoided.

Pulmonary Ventilation during Bypass

It is evident that during total bypass of the heart and lungs, ventilation of the lungs to provide oxygen and to eliminate carbon dioxide is not necessary. In the cyanotic patient with a large bronchial arterial flow of blood through the pulmonary capillaries, ventilation of the lungs during bypass is probably not harmful, although it could be expected to reduce carbon dioxide tension and raise the pH of the blood. In the acyanotic patient with a small bronchial arterial flow, pulmonary ventilation is obviously not necessary, and conceivably might be deleterious if it produced significant changes in the composition of the alveolar gases. Vigorous ventilation of the lungs in an acyanotic patient during bypass, with only a small flow of blood through some of the pulmonary capillaries from the bronchial arteries, would certainly reduce the normal carbon dioxide tension of the alveolar gas from 40 mm. Hg to almost zero, unless carbon dioxide were added to the ventilating gas. If, as is frequently the case, the ventilating gas is oxygen, ventilation during the period of bypass would raise the tension of oxygen in the alveolar gas from its normal level of 90 or 100 mm. Hg to the neighborhood of 700 mm. Hg. Finally, if a high gas flow, nonrebreathing technic were employed, harmful drying effects might be produced on the mucous membrane lining the tracheobronchial tree, as well as on the extremely thin cells of the alveoli themselves.

It seems reasonable to avoid these possibly deleterious changes in the water vapor and other gas concentrations of alveolar air by omitting pulmonary ventilation during bypass in the acyanotic patient. Suggestive evidence that such changes are deleterious to the function of the lungs in the postoperative period was obtained in our laboratory several years ago in experiments on normal dogs.[46] The right and left lungs were ventilated separately, but equally, by appropriate endobronchial technics, and the oxygen consumption of each lung was measured with the thorax open. The pulmonary artery of 1 lung was then occluded for a period of 1 hour, while the lungs were ventilated as before. Following release of the occlusion, the oxygen consumption of each lung was again measured. In the majority of experiments, the oxygen consumption of the lung in which the pulmonary artery had been occluded fell below the preocclusion measurement. After a period of 2 to 4 hours, the oxygen consumption of this lung tended to return to its previous level. On the other hand, when the lung with the occluded pulmonary artery was held stationary in an inflated position, the decline in oxygen consumption was not observed in the postocclusion period. These experiments suggest that ventilation of a lung without blood flow through the pulmonary artery may produce at least temporary impairment of pulmonary function. Therefore, while ventilation of the lungs of cyanotic patients during bypass may not be harmful, in the acyanotic patient, such ventilation may contribute to postoperative pulmonary dysfunction.

Atelectasis and Pulmonary Inflation

It is generally considered advisable to avoid prolonged complete collapse of the lungs during thoracic operations because, among other reasons, it becomes difficult to reinflate fully the lungs, and to do so excessively high inflationary pressures must be employed. If, then, the lungs are not ventilated during bypass, it is probably advisable to keep them inflated, though stationary. The degree of inflation probably need not be more than that existing in the normal position of expiration. The lungs then will not be tense and will not interfere with surgical exposure of the heart.

Postoperative Aids to Pulmonary Function

If all the precautions outlined above are taken, the patient's pulmonary function dur

ing the first few hours, or even the first day or 2 after operation, may still not be adequate to avoid hypoxemia and hypercapnia. This may be true, even though the usual postoperative measures to aid pulmonary function are employed. These measures include the breathing of a moist atmosphere enriched with oxygen, a tracheostomy to decrease respiratory dead space, and the encouragement of deep breathing by the alleviation of pain by drugs. The use, where possible, of median sternotomy and unilateral thoracotomy, which are less painful with respiration than the usual transverse thoracotomy, results in less impairment of respiratory excursions. In the experience of our group, the most important single means of aiding pulmonary function in the postoperative period is the use of intermittent positive pressure breathing. Not only is ventilation immediately improved, but secretions in the tracheobronchial tree are cleared by the great velocity of gas flow during the early part of expiration. Further study of this interesting field of postoperative pulmonary function is indicated.

Length of Perfusion

If an extracorporeal blood circuit exactly duplicated the functions of the heart and lungs, then, theoretically, there would be no limit to the period of time that such an apparatus could be used to substitute for these natural functions. Unfortunately such is not the case. Harmful phenomena occur in the extracorporeal blood circuit, or arise from the method of connecting the vascular system of the subject to the extracorporeal circuit, so that there is a limit to the time during which an extracorporeal circulation can be used safely. Much remains to be learned concerning these phenomena and their prevention.

Partial bypass of the heart and lungs can be tolerated by animals for periods of 4 and 5 hours with low mortality, whereas total bypass with open cardiotomy for a period of 2 hours in dogs results in a 50 per cent mortality.[47] Undoubtedly with both partial and total bypass, the harmful phenomena that occur in the extracorporeal circuit are cumulative, and finally reach such a degree that they can no longer be tolerated by the organism. When the same connections to the vascular system of the subject are used, there are 2 major differences between partial and complete bypass of the heart and lungs. The first is that in partial perfusion, only a part of the blood reaching the arterial system has passed through the extracorporeal circuit, and thus it will take a longer time for the harmful phenomena to become lethal. The second major difference is that in total bypass, blood no longer flows through the pulmonary capillaries except for the small component entering them by way of the bronchial arteries.

The measurable harmful phenomena that occur in the extracorporeal circuit are surprisingly few. They consist almost entirely in damage to the corpuscular elements of the blood. In brief, these phenomena consist of a gradually progressive hemolysis, a drop in the number of white blood cells to perhaps a fifth of their former concentration, and a sharp and profound thrombocytopenia. The 2 latter phenomena occur rapidly with only a very slow further decline. The hemolysis is less rapid, but exhibits the same general type of curve. The observed phenomena may be related to the age of the individual corpuscular elements, especially as regards resistance to trauma of the erythrocytes. However, no adequate data exist to support this hypothesis. It might well be studied by tagging the corpuscular elements with radioactive isotopes.

The lung has long been known to be an efficient filter for the blood. Undoubtedly other capillary beds act in a similar fashion, but no other capillary bed in the body filters all of the blood. Some of the destroyed leukocytes and thrombocytes very likely remain attached to the internal lining of the extracorporeal circuit. The free hemoglobin is removed largely by the reticuloendothelial system.

In partial bypass, no detectable alteration of the blood occurs consistently, aside from destruction of the cellular elements. With total bypass, as mentioned earlier, inadequate oxygenation of the tissues may result in metabolic acidosis if the blood flow and blood

pressure fall below a certain minimum level. No other changes are consistently detectable in the blood. For example, there is no significant alteration in the level of fibrinogen during 2 hours of total bypass in animals, and only 2 of 16 animals exhibited measurable degrees of fibrinolysis.[47]

Summary

The experimental use of extracorporeal blood circuits during the past 24 years, and the clinical experience of the past 5 years, have posed many interesting physiologic problems. A few of these have been solved for practical purposes by much excellent recent investigation. Among those remaining to be solved the following might be listed:

On the initiation of total bypass of the heart and lungs by an extracorporeal circulation, is the blood flow to the body increased or decreased in relation to the cardiac output before bypass? Available technical methods exist to answer this question.

The volume of blood in the lungs before, during, and after total bypass should be determined. Technics are available to accomplish this.

The rate of blood flow through the major branches of the aorta should be measured before and during bypass with a normal direction of flow in the aorta, as well as with reversal of flow. The recent perfection of square-wave electromagnetic blood flow recorders makes this a relatively simple task.

Adequate studies have been performed to indicate the importance of maintaining a nearly normal blood flow and pressure during perfusion. Further investigation is needed to determine how long high oxygen tensions may be maintained in the blood without toxicity. The conflicting evidence concerning the relation of metabolic to respiratory acidosis should be resolved.

Induced cardiac arrest requires a great deal of further study. What is the best method of producing arrest, and how long and under what circumstances can it be safely maintained?

Finally, the subject of postoperative pulmonary dysfunction needs much further study. The results of such study may well lead to a reduced morbidity and mortality following operations involving open cardiotomy with the extracorporeal circulation.

Summario in Interlingua

Le uso experimental de circuitos extracorporee de sanguine durante le passate 24 annos e le experientia clinic del passate 5 annos ha sublevate multe interessante problemas physiologic. Plures inter illos esseva resolvite, in tanto que lor signification practic es concernite, per multe excellente investigationes in le recente passato. Quanto al problemas que remane a solver, le sequentes merita esser listate:

Post le transferimento complete del functiones cardiorespiratori al circulation extracorporee, es le fluxo de sanguine a in le corpore augmentate o reducite in comparation con le rendimento cardiac ante le institution de ille transferimento? Le methodos technic pro resolver iste question es jam disponibile.

Le volumine de sanguine in le pulmones ante, durante, e post le transferimento complete deberea esser determinate. Le technicas pro effectuar tal determinationes existe.

Le intensitate del fluxo sanguinee a transverso le major brancas del aorta debe esser mesurate ante e durante le transferimento, con fluxo normal in le aorta e etiam con fluxo revertite. Le recente perfection de electromagnetic fluxometros a undas quadrate pro le mesuration de fluxos sanguinee rende iste problema relativemente simple.

Studios adequate ha essite effectuate, demonstrante le importantia de mantener un quasi normal fluxo e tension de sanguine durante perfusiones. Investigationes additional es requirite pro determinar durante quante tempore alte tensiones de oxygeno pote esser mantenite in le sanguine sin effectuar toxicitate. Le contradictiones in le datos concernente le relation inter acidosis metabolic e acidosis respiratori debe esser resolvite.

Inducite arresto cardiac require un grande concentration de studios additional. Qual methodo es le melior pro effectuar arresto cardiac, e durante quante tempore e sub qual conditiones pote illo esser mantenite sin risco?

Finalmente, le thema del post-operatori dysfunction pulmonar require multe studio additional. Le resultatoes de tal studios va forsan causar un reduction del morbiditate e mortalitate post operationes in que cardiotomia aperte es interprendite con le adjuta de un circulation extracorporee.

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Plasma Catechol Amine Concentrations in Myocardial Infarction and Angina Pectoris

By P. C. GAZES, M.D., J. A. RICHARDSON, PH.D., AND E. F. WOODS, PH.D.

Urinary catechol amines have been shown to be increased in a few cases of acute myocardial infarction. The present study shows that patients with acute myocardial infarction and with angina pectoris (after exercise) have an increase in plasma catechol amines as compared to normal subjects before and after exercise and as compared to patients with noncardiac types of pain. The significance of these findings is discussed.

THERE have been many reports that the adrenergic catechol amines (epinephrine and norepinephrine) cause a wastage of oxygen by the heart muscle that exceeds the simultaneous oxidative energy requirements for mechanical work. Recently, however, Katz[1] suggested a "stress-adapting mechanisms" related to the catechol amines that appears to make the heart more efficient in the utilization of oxygen in the experimental animal. In either event with cases of myocardial infarction or angina pectoris an excess of these amines may be of clinical significance.

Raab,[2, 3] utilizing a modification of Shaw's colorimetric method, showed an increase in blood catechol amines in 7 patients with angina after exercise as compared to 14 normal cases. However, this method has subsequently been shown to be insufficiently sensitive to measure minute quantities in blood.[4] Nuzum and Bischoff[5] found increased amounts of epinephrine in the urine of 2 patients with myocardial infarction and 1 of these showed such amounts on 4 occasions. Raab and Gigee,[6] on the other hand, were unable to detect grossly abnormal total urinary catechol excretion in patients with myocardial infarction, arterial hypertension, congestive failure or in states of emotional tension. They[7] performed colorimetric determinations of total catechol amine content and bioassay of norepinephrine and epinephrine separately in 85 autopsied human hearts. Significant increases above normal were found in cases of recent myocardial infarction and in congestive failure. Bloodworth and von Haam,[8] using a similar colorimetric method, determined the tissue concentration of catechol amines in 100 autopsied human hearts. Cardiovascular diseases showed low or normal values. Five of these were cases of myocardial infarction. The literature contains numerous papers dealing with the tissue concentration of catechol amines in normal animal hearts, but no data are available for the diseased state in animals.

Because of the variability of these reports in heart tissue and in the urinary excretion of catechol amines and the limited investigations of plasma concentrations, the present study was performed to correlate plasma levels in cases with myocardial infarction and in those with angina pectoris.

METHOD

Plasma catechol amine levels were determined fluorimetrically by the method of Weil-Malherbe and Bone,[9] as modified by Richardson et al.[10] This method is capable of measuring plasma levels as low as 0.25 μg. of epinephrine and 0.5 μg. of norepinephrine per liter of plasma. When known amounts of the amines are added to plasma, the mean recovery[10] of epinephrine is 93.4 per cent ± 11.5, and of norepinephrine 90.3 per cent ± 9.9. With regard to the specificity of the method, Weil-Malherbe and Bone[9] found that the fluorescent substances in blood are "identical with adrenergic amines in their affinity to amine oxidase, in Rf values, and the fluorescent spectra of their derivatives." Moreover, in this laboratory in instances of adrenal medullary stimulation where one would expect to observe increases in circulating epinephrine, such was the case;[16] increments in norepinephrine were noted in splenic

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TABLE 1.—*Catechol Amines (μg./L. plasma) in Cases of Acute Myocardial Infarction*

Patient no.	First 36-hr. period		After 72 hrs.	
	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
1	9.10	1.00	2.26	1.07
2	6.34	.49	1.97	.19
3	3.48	.90	1.39	.51
4	7.50	.42	2.21	.81
5	4.32	.47	3.16	.63
6	4.90	2.84	3.60	.47
7	3.42	.45	1.12	.39
8	3.04	.59	1.04	.15
9	5.22	.11	1.73	.43
10	4.18	.78	2.19	.17
11	4.10	.05	1.39	.51
12	5.55	.70		
13	7.50	1.30		
Mean	5.28	.78	2.01	.48

blood during electrical stimulation of the splenic nerve. Although fluorescent compounds are found when ethylenediamine is condensed with certain agents, notably 3,4-dihydroxyphenylethylamine (a probable precursor of norepinephrine) and 3,4-dihydroxyphenylacetic acid, this does not detract from the specificity of the method as used here, since the presence of these chemicals has not been demonstrated in plasma. Epinephrine and norepinephrine determinations were made within the first 36 hours in 13 cases of acute myocardial infarction, all with definite electrocardiographic changes and other characteristic findings. None of these patients manifested cardiogenic shock. In 11 of the cases, levels were also determined after 72 hours and in 10 of them serum transaminase levels were obtained simultaneously. Recognizing the increased sympathetic activity produced by opiates,[11] no narcotics were administered in 11 cases for 12 to 24 hours prior to the determinations. In the other 2 patients opiates were given prior to the first and second determinations. Plasma amine levels were also determined in 6 cases with a noncardiac type of pain. In 3 of these patients pain was due to trauma and in the other 3 to abdominal pathology.

Epinephrine and norepinephrine levels were studied also in 12 patients with angina pectoris and in 7 normal individuals. The normal subjects were matched to the patients with angina in their other characteristics, such as age, dietary habits, and body weight. Levels were determined before and after exercise using a double 2-step Master's test. When the patients with angina developed pain prior to completion of their required exercise, the levels were determined at this point. Levels were also obtained in 3 of the patients with angina before and during cigarette smoking.

TABLE 2.—*Catechol Amines (μg./L. Plasma) in Normal Subjects before and after Exercise*

Subject no.	Before exercise		After exercise	
	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
1	3.09	.28	3.99	.21
2	2.86	.01	2.58	.15
3	2.43	.09	2.17	.01
4	2.55	.01	3.09	.00
5	3.35	.36	3.14	.15
6	1.35	.50	1.47	.68
7	1.40	.26	1.25	.45
Mean	2.43	.22	2.53	.24

TABLE 3.—*Catechol Amines (μg./L. Plasma) in Cases with Noncardiac Pain*

Patient no.	Norepinephrine	Epinephrine
1	1.53	.70
2	1.17	.09
3	2.47	.35
4	1.21	.30
5	1.25	.06
6	3.44	.89
Mean	1.85	.40

RESULTS

Table 1 compares the plasma levels of the catechol amines in 11 cases of acute myocardial infarction taken within the first 36-hour period with those after 72 hours. The level of norepinephrine was higher in all cases in the first 36-hour period and the epinephrine results were variable. Single initial levels of amines were determined in 2 other cases. In all 13 cases the initial levels of norepinephrine were significantly greater ($p < .001$) than in the 7 normal subjects of table 2. In 7 cases the initial levels of epinephrine were greater than in the 7 normals ($p < .01$). The values for the 6 patients with noncardiac types of pain (table 3) were in the normal range. Figure 1 compares the plasma catechol amine levels in 10 of the cases of myocardial infarction with serum transaminase levels drawn simultaneously within the first 36-hour period. A significant linear relationship was found between norepinephrine and transaminase, the correlation coefficient being 0.80 ($p < .01$). The correlation coefficient with epinephrine as one of the parameters was 0.04, indicating no significance ($p > .1$).

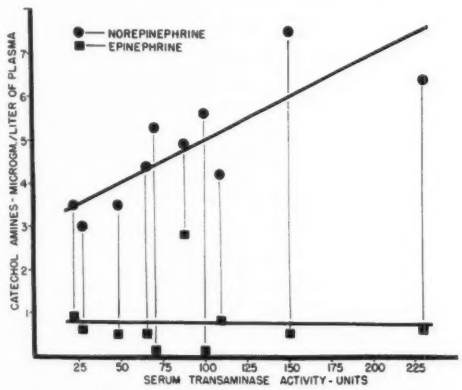

FIG. 1. The relation of catechol amines (μg./L. plasma) to serum transaminase (*abscissa*) determined within the first 36-hour period of 10 patients with acute myocardial infarction.

In table 4 catechol amine levels of 12 cases of angina pectoris are compared before and after exercise. Norepinephrine increased in 8 cases after exercise whereas epinephrine increased in 5. Statistically there was a marked difference in values before and after exercise (norepinephrine, $p < .001$; epinephrine, $p < .01$). In the 7 normal subjects (table 2) there were no significant increases after exercise. In 2 of the 3 cases of angina (table 5) total amines increased during cigarette smoking.

DISCUSSION

The liberation of adrenal medullary hormonal material, the bulk of which is epinephrine, into the blood stream and its utilization in the tissues occur under a variety of stressful situations, such as muscular exercise, emotional tension, pain, and under the influence of a reflex mechanism which originates in the carotid sinus. Norepinephrine constitutes up to 30 per cent of the hormone content of the adrenal medulla and of its secretion, and is elaborated by postganglionic adrenergic nerve endings. It is also probably the immediate precursor of epinephrine. A large part of the sympathomimetic substances present in the normal myocardium has been identified as norepinephrine.[12] It constitutes 75 to 90 per cent of the sympathomimetic amines of the heart, the remainder being largely epinephrine. Richardson and Woods[13] showed that

TABLE 4.—*Catechol Amines (μg./L. Plasma) in Cases of Angina Pectoris before and after Exercise*

Patient no.	Before exercise		After exercise	
	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
1	2.46	.78	12.10	2.48
2	1.67	.29	1.27	.45
3	1.39	.51	1.43	.46
4	3.93	.11	8.33	.04
5	2.23	.80	5.17	.86
6	3.19	.44	7.43	1.28
7	3.55	.44	4.00	1.97
8	3.18	1.25	7.10	3.27
9	2.54	1.42	4.82	1.29
10	1.41	.74	1.49	.93
11	1.44	1.25	7.75	.02
12	3.40	.07	5.75	.10
Mean	2.53	.68	5.55	1.09

TABLE 5.—*Catechol Amines (μg./L. Plasma) in Cases of Angina Pectoris before and during Smoking*

Patient no.	Before		During	
	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
1	1.87	.11	1.71	.45
2	3.69	.14	7.52	.56
3	2.76	.21	4.21	.06

large doses of acetylcholine produced substantial increments in the concentration of norepinephrine in the perfusion fluid from isolated rabbit hearts. Epinephrine values remained essentially unchanged.

The increased plasma concentrations of norepinephrine and epinephrine in many of the cases of myocardial infarction and angina after exercise suggest liberation of these amines not only from the adrenal medulla but also probably in part from the myocardium and coronary vessels in these diseased states. This observation may be of significance not only as to prognosis but also as to therapy. "Mechanism deaths," namely ventricular fibrillation, are often seen in such cases in spite of prophylactic anti-arrhythmic drugs such as quinidine and procaine amide. Furthermore, these drugs by decreasing myocardial irritability may also further depress myocardial contractility and so present an increasing hazard. Since arrhythmias usually do not begin until several hours after infarction, Harris[14] believed that sympatho-adrenal substances liberated during necrosis of the

muscle may act as local excitatory factors to produce them. Gilbert et al.[15] recently have shown the degree to which catechol amines are capable of inducing ectopic pacemaker action. Sudden unexpected cardiac deaths from ventricular fibrillation have been observed in a number of cases in which autopsy revealed various degrees of coronary sclerosis but no significant myocardial lesion. Many of these patients had an intact ventricular myocardium and sufficient coronary flow to permit them to live comfortable and productive lives.

Anoxia with accumulation of lactic acid may be associated with stimulation of chromaffin tissue within the heart and release of epinephrine and norepinephrine. This is a possible mechanism, since lactic acid is a potent stimulant to the chromaffin tissue of the adrenal medulla as evidenced by marked increments in circulating catechol amines when it is injected into the adrenal circulation.[16] Pain of noncardiac causes did not produce elevation of these amines. Reflex discharge of these amines due to shock was ruled out, since none of the patients with myocardial infarction manifested signs of shock.

Since there is reason to believe these amines intensify the anginal pain in patients with coronary sclerosis, a reduction of circulating concentrations of the amines or a blockade of their effects appears as another rational therapeutic approach to angina pectoris. The most practical method is that of physical rest and mental relaxation to diminish sympathetic stimulation. Exposure to cold temperatures, heavy meals, and excessive tobacco smoking should likewise be avoided, since they can be expected to cause increased discharges. Thoracic sympathetic ganglionic block or sympathectomy and sympatholytic drugs have been used with some encouraging results. X-ray of the adrenal glands and later total ablation of the thyroid gland by drugs, surgery, or radioactive iodine (I^{131}) have also been utilized. Thyroid hormones intensify both the physiologic and toxic adrenergic action on the heart. Although nitroglycerin may have a specific anti-adrenergic action on the heart muscle in addition to its coronary dilator effect[17] it more probably acts largely by reducing peripheral resistance and thus reducing the work load of the heart.[18] Acute stimulation of the vagus by pressure on the carotid sinus has been recommended by Levine to terminate anginal attacks with occasional striking results. It is described as initiating an anti-adrenergic, oxygen-sparing effect upon myocardial metabolism.[19] Freedberg and Riseman[20] presented observations consistent with the hypothesis that stimulation of the carotid sinus induces relief of cardiac pain by interruption of sympathetic reflex arcs or sensory pathways. Recently Paasonen and Krayer[21] showed that administration of reserpine to heart-lung preparations of the dog leads to a marked decrease of norepinephrine content of the heart, but no decrease in epinephrine.

Summary

Norepinephrine plasma levels were significantly increased in 13 cases of myocardial infarction and in 7 of these there was also a significant increase of epinephrine as compared to 7 normal subjects. There were no comparable increments of the amines in 6 patients with noncardiac types of pain.

In myocardial infarction there was a positive correlation of norepinephrine and transaminase levels, but there was no such relationship with epinephrine and transaminase.

In 12 cases of angina pectoris norepinephrine increased in 8 cases after exercise, whereas epinephrine increased in only 5. There was no significant change with exercise in the 7 normal subjects.

It is believed that these increases in plasma catechol amines in patients with myocardial infarction and angina pectoris may play a significant part in therapy and prognosis.

Acknowledgment

We wish to express our thanks to Dr. R. P. Walton for helpful advice and criticism in the preparation of this paper.

Summario in Interlingua

Le nivellos de norepinephrina in le plasma esseva significativemente augmentate in 13

casos de infarcimento myocardial, e in 7 de illos il habeva etiam un augmento significative de epinephrina in comparation con 7 subjectos de controlo. Nulle comparabile augmentos del aminas esseva constatate in 6 patientes con typos non-cardiac de dolor.

In infarcimento myocardial, il existeva un correlation positive del nivellos de norepinephrina con illos de transaminase. Nulle tal correlation esseva trovate inter epinephrina e transaminase.

In 12 casos de angina de pectore, le norepinephrina montava in 8 post exercitio, le epinephrina in solmente 5. Nulle significative alteration esseva notate post exercitio in 7 subjectos de controlo.

Es opinate que iste augmentos de catecholaminas in patientes con infarcimento myocardial e angina de pectore ha possibilemente un rolo significative in therapia e prognose.

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Arteriovenous Fistula of the Kidney

New Observations and Report of Three Cases

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ARTERIOVENOUS fistulas of the kidney or renal vessels are probably not so rare as the small number of reported cases suggest. The fact that all but 2 of the total of 12 cases appearing in the literature are recently reported (within the past 11 years) lends support to this contention.

To this total of 12, we should like to add the following 3 cases that were observed at the Mayo Clinic between the years 1954 and 1957.

REPORT OF CASES

*Case 1.** This patient was a man 42 years of age when last seen at the clinic in 1955. The patient was first seen here in 1950, at which time he complained of fatigue, sweating, palpitation, and a feeling of stimulation and nervousness. He was clinically euthyroid, and his blood pressure was 150 mm. of mercury systolic and 90 mm. diastolic. His history indicated that he had been shot at close range in a hunting accident at age 14 years. The 22-caliber bullet entered his trunk anteriorly in the region of the liver. Gross hematuria occurred for 2 weeks, during which time the patient was in bed with drains in the hepatic region. A roentgenogram of the lumbar vertebrae showed the bullet lodged between the bodies of the first and second lumbar vertebrae with post-traumatic ankylosis bridging the area.

Since the roentgenogram of the chest in 1950 showed cardiac hypertrophy and the history of trauma was known, evidence of an arteriovenous fistula was sought in an attempt to explain the enlargement of the heart. A loud continuous bruit, loudest in the midaxillary line, was found over the upper part of the abdomen on the right.

The urine was normal, but an excretory urogram revealed marked distortion of the renal calyces. Results of the sulfobromophthalein (bromsulphalein) test of liver function were negative.

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*A report on this case appeared in an exhibit at the meeting of the American Medical Association in June 1955.

In an attempt to obtain evidence supporting the diagnosis of renal arteriovenous fistula, limited cardiac catheterization was carried out. Unfortunately, the catheter could not be made to enter the right renal vein, and evidence of arterialization of the blood was not encountered in the inferior vena cava, so proof of an arteriovenous fistula of the kidney could not be obtained (table 1). Nevertheless, the patient was considered to have an arteriovenous fistula of the right kidney and surgical exploration was advised with an alternative of continued periodic observation.

The patient returned 4 years later (1954) with the same complaints, but increased in severity. The enlargement of the heart had increased. The electrocardiogram showed changes consistent with early left ventricular hypertrophy. At catheterization, indicator-dilution studies showed recirculation time of 12 seconds as compared to a normal value of approximately 21 seconds. The cardiac output was increased as compared to the 1950 studies (table 1). An aortogram showed a greatly enlarged and tortuous renal artery terminating in what appeared to be an aneurysmal sac (fig. 1). Right nephrectomy was carried out.

Pathologic examination revealed an arteriovenous fistula with the renal artery and vein entering a common aneurysmal sac located at the hilus of the kidney. The narrowest portion of the arteriovenous fistula was 4 mm. in diameter (fig. 2).

Seven months later the patient returned stating that he felt normal for the first time in many years. At that time, cardiac catheterization yielded normal findings except for some slowing in the systemic recirculation time (table 1). Blood pressure was now normal, 128/86, and there was a rather striking reduction in size of the heart (fig. 3). The abnormal electrocardiographic pattern had disappeared.

Case 2. The patient, a 30-year-old woman, was admitted to the hospital in 1957 because an arteriovenous fistula of the left kidney was suspected. At the age of 4 years, she had been run over by the wheel of a wagon but apparently had sustained no significant injury. A heart murmur had been heard at an examination when she was in her early teens. She was married at 19 years of age and in the next 10 years had an unremarkable health record, which included 4 uneventful pregnancies.

TABLE 1.—*Cardiac Catheterization in Case 1*

	1950		1954		1955	
	Output (L./min.)	Index	Output (L./min.)	Index	Output (L./min.)	Index
On air			7.7	3.8	5.9	2.9
On oxygen	8.0	3.9	10.7	4.9	6.3	3.0
Recirculation time		—	12 sec.		31 sec.	
Radial artery pressure (mm. Hg)		—	173/84		137/80	

The present illness appeared to coincide with the beginning of her fifth pregnancy in September 1956. About this time she began to be weak and fatigued easily, and she had episodes of left upper abdominal pain. In January 1957, tachycardia, edema of her ankles, and an apical systolic cardiac murmur developed. The next month she was hospitalized for treatment of congestive heart failure. Continuous treatment for this condition was necessary until labor was induced and a normal child was delivered on May 22, 1957. During the last 4 months of pregnancy, a bruit had been heard over the left flank. Since delivery, the patient had remained virtually at rest in bed.

On examination the blood pressure was 180/80; the pulse rate during rest was 120 beats per minute. Funduscopic examination of the eyes revealed narrowing, grade 2, and focal constrictions, grade 1 (on a grading basis of 1 to 4), of the retinal arterioles, but no sclerosis was discernible. Examination of the heart revealed gross cardiac enlargement and a soft systolic apical murmur. A loud bruit and thrill were found in the left upper part of the abdomen anteriorly, laterally, and posteriorly. These were continuous and were accentuated during systole. The point of maximal intensity was immediately over the kidney posteriorly.

Laboratory examinations gave the following results: The urine contained albumin, grade 3; the blood showed 8.6 Gm. of hemoglobin per 100 ml. and 18 mg. of urea per 100 ml. An excretory urogram, cystoscopy, and a left retrograde pyelogram showed a nonfunctioning left kidney that appeared about half the size of its mate. A roentgenogram of the chest showed cardiac enlargement.

In order to delineate the nature of the suspected arteriovenous communication, a special catheterization procedure was carried out. The right atrial pressure was elevated, being 15/10 mm. Hg. The oxygen saturation of blood withdrawn from the superior vena cava was 61 per cent and that withdrawn from the inferior vena cava at the junction of the iliac veins was 64 per cent; both these values were below normal. The oxygen saturation of blood withdrawn from the inferior vena cava in the region of the orifices of the renal veins, however, was 95 per cent. The catheter was introduced into what was apparently the left renal vein, and blood withdrawn from this site had an oxygen saturation of 97 per cent, which was not significantly different from blood simultaneously withdrawn from the radial artery. A catheter was introduced into the right femoral artery and advanced to the level of the diaphragm. After injections of dye into the aorta at the diaphragm, dye-dilution curves were recorded simultaneously from the radial artery and from the "right-heart" catheter when its tip was in the left renal vein and after withdrawal to the inferior vena cava at the diaphragm. The contour of the dye curves indicated a rapid recirculation time (11 seconds), as is typical of patients with large arteriovenous fistulas. The dye curves recorded from the left renal vein and inferior vena cava indicated a large arteriovenous fistula in or near the left kidney. A selective angiocardiogram was made by injecting contrast media through a catheter, whose tip was in the right renal artery. The picture was consistent with an arteriovenous fistula at the hilus of the left kidney. Estimation of the size of the shunt based on saturation data indicated that 69 per cent of the inferior vena caval blood was from the shunt.

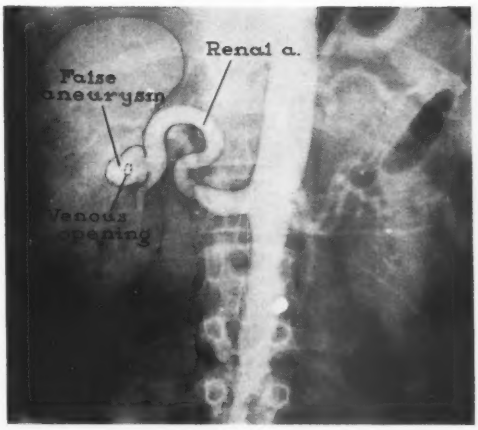

FIG. 1. Case 1. Aortogram in 1954 showing a greatly enlarged and tortuous renal artery terminating in an aneurysmal sac.

At the time of nephrectomy the left kidney was found to be about half normal size and adherent to surrounding structures. The renal artery approached the kidney in a downward direction and communicated directly with the renal vein in the

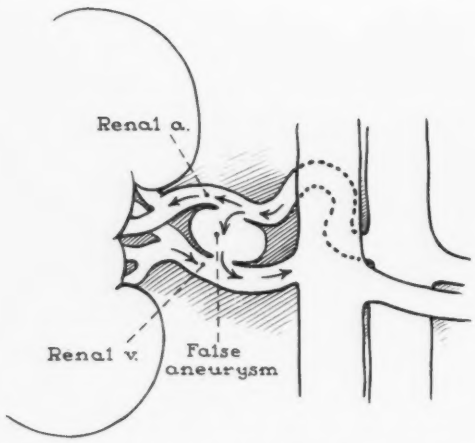

FIG. 2. Case 1. Findings at pathologic examination.

hilus of the kidney. There was a saccular dilatation of the renal vein about the size of a golf ball, and the remainder of the visible portion of the renal vein was at least three times normal size and thickened. The ostium of the arteriovenous fistula was 8 mm. in diameter.

The patient's postoperative course was uneventful. Her blood pressure in the immediate postoperative period was 130/80.

Case 3. A 39-year-old woman was referred to the clinic by her physician, Dr. James R. Machan of Fort William, Ontario, in April 1955, because of hypertension of 3 years' duration, cardiac enlargement with early cardiac failure, and an abdominal mass that was considered to be an arteriovenous aneurysm. She mentioned also severe frontal headaches, weakness, and easy fatigability. She denied urinary symptoms.

The pertinent findings at physical examination included a precordial systolic murmur, grade I, and evidence of cardiac enlargement. The blood pressure averaged 192/105. A firm palpable mass was present in the left upper quadrant of the abdomen, and over the mass a thrill and a loud continuous bruit with systolic accentuation were noted. The bruit radiated from the mass and could be detected throughout the abdomen, the left loin, and the chest. Examination of the ocular fundi disclosed narrowing of the retinal arterioles, grade 2, and areas of focal constrictions and hypertensive sclerosis, grade 1.

Laboratory examinations of the urine and blood (including blood urea) yielded normal findings. Roentgenographic examination of the thorax disclosed cardiac enlargement, and the electrocardiogram was consistent with left ventricular hypertrophy.

Study of the upper part of the urinary tract by excretory urography and left retrograde pyelography disclosed a rounded enlargement of the upper pole of the left kidney, and the upper calyx appeared flat, elongated, and broad. The infundibulum leading to the upper calyx was broad and irregular with a hook-shaped deformity in a branch of the middle calyx (fig. 4). An aortogram disclosed irregular pooling of medium over the region of the left kidney (fig. 5). A clinical diagnosis of hypernephroma or benign vascular tumor with arteriovenous fistula was made, and surgical intervention was advised.

Surgical exploration revealed a vascular mass occupying the hilus and upper pole of the left kidney. The left renal vein was strikingly enlarged, and the renal artery was divided into several different branches. Nephrectomy was performed. Examination of the excised specimen (fig. 6) disclosed a hypernephroma, 10 cm. in its greatest diameter, occupying the upper pole of the kidney. The arteriovenous fistula consisted of branches of the renal artery and vein which entered an aneurysmal sac that measured 6 by 6 cm. and was situated in the region of the hilus. Two large venous pools that drained into the renal vein were situated within the neoplasm.

A roentgenogram of the thorax made on the tenth postoperative day disclosed a distinct decrease in size of the cardiac shadow. Hypertension persisted, however, and a value of 170/110 was noted.

In response to inquiry the patient's physician in her home locality stated that he had examined her in January 1958. She had remained well during the intervening 3 years, had gained 15 pounds and was free of symptoms. The blood pressure remained elevated to 200/100. Examination of the ocular fundi, however, yielded normal findings. The cardiac enlargement had decreased.

CLASSIFICATION

Because of the considerable inaccuracy and ambiguity in the titles of articles dealing with intrarenal or parenchymal shunts, fistulas of the renal artery and vein, and fistulas in the stump of the renal vessels following nephrectomy, the following simple classification is proposed. It is based on the location and the nature of the communication: I. Arteriovenous fistula of the kidney. II. Postnephrectomy arteriovenous fistula.

The term "arteriovenous fistula of the kidney" would include those fistulas occurring within the kidney substance itself as well as those of extrarenal origin involving the renal

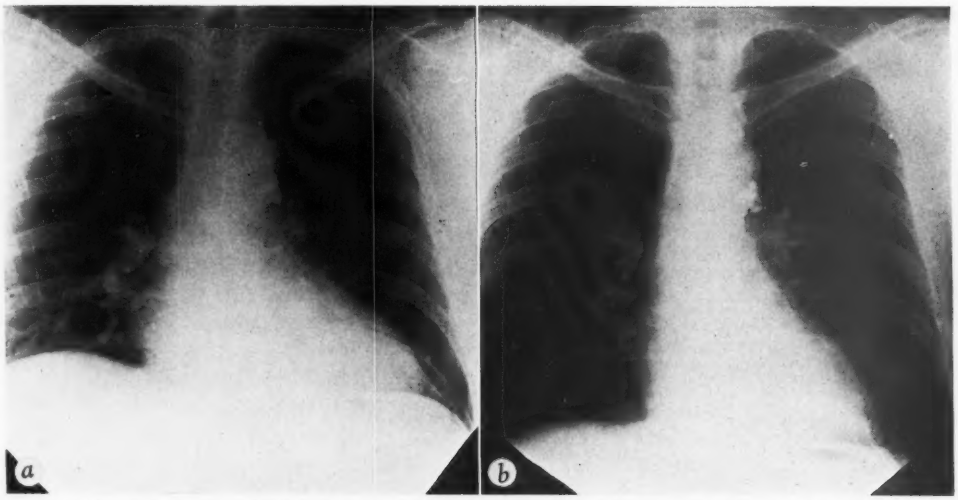

FIG. 3. Case 1. The thorax. *a.* In 1954 showing enlargement of the heart. *b.* In 1955 after operation. The rather striking reduction in the size of the heart should be noted.

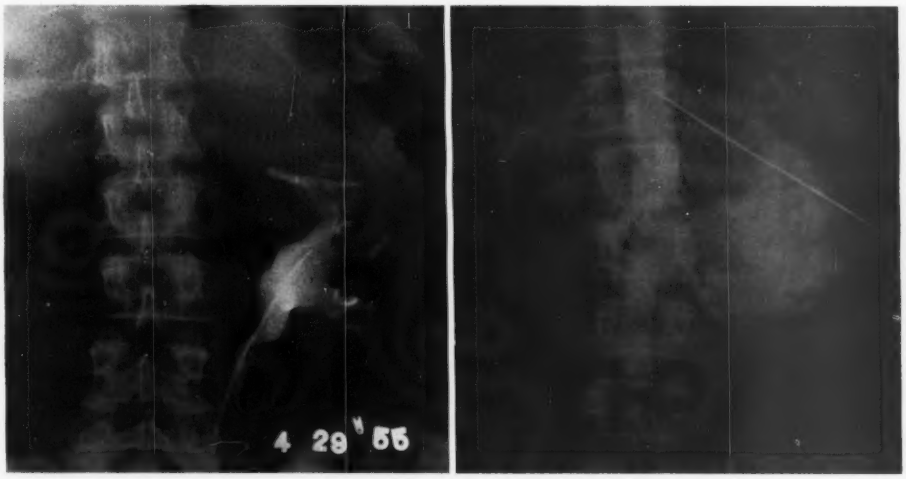

FIG. 4 *Left.* Case 3. Retrograde pyelogram of the left kidney showing deformity of the calyces.

FIG. 5 *Right.* Case 3. Aortogram showing irregular pooling of medium over the left renal area.

artery and vein. An aneurysmal sac is commonly present as part of the fistulous tract.

Although the term, "arteriovenous fistula of the renal vessels," might seem satisfactory, it would include fistulas occurring in the stumps of the renal vessels following nephrectomy,[1] and could therefore have 2 entirely different meanings. The term, "postnephrectomy arteriovenous fistula," of course, implies a fistula between the stumps of the renal artery and vein.

The need for some standardization can quickly be appreciated by reviewing the literature because of several, almost completely misleading titles.[1-3] The term, "arteriovenous aneurysm," commonly has been employed,[4-8]

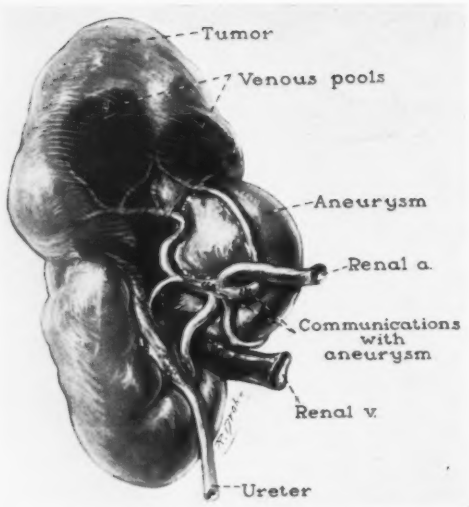

FIG. 6. Case 3. Pathologic findings.

but since the fundamental lesion is a fistula, not an aneurysm, "clarity is lost and confusion is served by maintenance of other terms which have been used to indicate some of the manifestations of abnormal arteriovenous communication."[9]

INCIDENCE

The scarcity of reports suggests that arteriovenous fistulas in the kidney or the renal vessels when the kidney is present are rare. Several cases included in previous reviews of the literature and listed in the *Quarterly Cumulative Index Medicus* have not been included in this review for one reason or another. In the case reported by Hollingsworth[1] the diagnosis was not confirmed. This case, along with 2 others, actually represents a postnephrectomy arteriovenous fistula. From the clinical and physiologic standpoint, such fistulas resemble peripheral rather than renal arteriovenous fistulas and should not be included in a discussion of the latter.

The case reported by Garritano and coworkers[10] is excluded also because the same case was reported by Kirby and associates[11] a year earlier.

The fact that 10 of the total 15 cases (including the present series) reported to date have been noted in the past 4 years indicates that arteriovenous fistulas of the kidney or renal vessels are much commoner than had previously been thought.

Since the bruits produced by these fistulas are easily heard, we should like to suggest that auscultation be carried out over the renal areas in patients who have unexplained cardiac enlargement, unexplained deformities of the kidney or renal pelvis or both, unexplained cardiac failure, and hypertension. In this way fistulas may be detected in their early stages.

ETIOLOGIC ASPECTS

The abnormal arteriovenous communications in the kidney and renal vessels in the 15 cases (including our 3 cases) were thought to be congenital in 6, and to be due to trauma in 6 and to malignant tumors in 3.

Concerning 5 of the 6 cases listed as traumatic in origin, there is little doubt as to the cause since, in 3, bullet wounds, in 1 a stab wound, and in 1 a surgical procedure involved the renal vessels. The cause was uncertain in only 1 of the 6 cases (table 2).

Of the 6 arteriovenous fistulas listed as being of congenital origin, 2 were intrarenal,[4, 14] and 4 were in the renal vessels.[2, 5–7] All 6 patients had fistulas that were aneurysmal in nature.

Simple aneurysm of the renal artery seems to be much commoner than arteriovenous fistula. To May 1955, 120 cases had been reported.[16] It is easy to visualize how such an aneurysm may erode its way into the renal vein while in the process of rupturing, with a fistula between the renal artery and vein as the final result. Additional support is given to this thesis by the fact that 2 of the 6 patients with congenital fistulas were free of symptoms until they were 60 years of age or older.[4, 5] It is well known that one of the factors leading to the development of symptoms from arteriovenous communications is the duration of the shunt. This makes survival until age 60 years most unlikely unless the fistula is of more recent origin.

TABLE 2.—*Summary of Cases in Literature*

Author	Date, age, sex	Presenting complaint	Symptoms and findings	Blood pressure (mm. Hg)	Cause	How diagnosed	Outcome: heart and blood pressure
Varela[7]	1928 28 M	Severe dyspnea	Enlarged heart, failure, bruit rt. flank	160/80	Congenital	At necropsy	Died
Rieder[6]	1942 29 M	Palpitation, dyspnea	Enlarged heart, failure, bruit rt. flank	220/120	Congenital	At operation	Normal; 125/90
Pearse and MacMillan[5]	1947 60 M	Hematuria	Not given	160/60	Congenital	At operation	?; 125/75
Adams[2]	1951 ?	?	Not stated	?	Congenital ?	?	Not stated
Hamilton et al.[12]	1953 29 M	Severe dyspnea, cough, fatigue	Marked pulm. edema, heart failure, bruit in left lumbar region	180/110 170/92	Adeno-carcinoma	At operation	Normal; 140/90
Pélot et al.[3]	1954 26 M	Dyspnea, cough	Heart greatly enlarged; gallop rhythm; bruit, grade 4 retinopathy	210/130	Bullet injury, 1952	At operation	Normal; 135/75
Vest[8]	1954 3 F	Hematuria	—	—	Nephro-lithotomy	At operation	—
Baron and Koenemann[13]	1955 5 F	Headaches	Hypertension, bruit in left flank	146/110	Stab wound	At operation	Normal; 120/80
Kirby et al.[11]	1955 22 M	Dyspnea, weakness	Enlarged heart, bruit	180/60	Bullet wound, 1952	By aortogram	Normal; 120/74
Slominski-Laws et al.[14]	1956 19 F	Dyspnea, edema	Heart enlarged	120/80	Congenital	By aortogram	Not stated
Myhre[15]	1956 66 F	Hematuria	Heart normal, bruit, pain in rt. flank	140/70	Adenocar-cinoma	By cardiac catheteri-zation and aortogram	—
Bohne and Henderson[1]	1957 63 M	Dyspnea	Heart enlarged, bruit	?	Congenital	From aortogram	Normal; (?)
This series Case 1	1954 42 M	Palpitation, fatigue, sweating	Heart enlarged, bruit	174/84	Bullet wound, 1926	At cathe-terization plus aorto-gram	Normal; 128/86
Case 2	1957 30 F	Abdominal pain, dyspnea	Heart enlarged, heart failure	180/80	Injury (?) 1931	At cathe-terization plus angio-gram	Normal; 130/80
Case 3	1955 39 F	Hypertension, lump in abdomen	Heart enlarged, heart failure	206/110 180/100	Hyperne-phroma	From aortogram	Elevated; 200/100

Further evidence is seen in our case 2. This patient was in good health until age 29 years when symptoms developed, which, within 3 months, progressed to marked congestive failure. Such a picture is inconsistent with the concept of a life-long arteriovenous fistula.

From the standpoint of renal carcinoma, it is probable that considerably more tumors result in abnormal arteriovenous shunts than the present figures would indicate. Careful auscultation with the stethoscope over the site of a renal tumor may well disclose a significant percentage of arteriovenous bruits. In the 3 cases of malignant tumor of the kidney[12, 15] in this series, including our case 3, erosion of the renal vessels by the tumor was the cause of the shunt.

Clinical Features

Many of the clinical features noted in the 15 cases of abnormal renal arteriovenous communication, which make up the world's literature to date, are summarized in table 2. Our 3 cases are included.

The most notable features are hypertension and cardiac enlargement with varying degrees of myocardial insufficiency. These 2 features, particularly the hypertension, tend to set these fistulas apart from arteriovenous fistulas in other parts of the body. Peripheral arteriovenous communications do not result in hypertension and do not commonly result in heart failure.[14] Hypertension is truly a hallmark of an arteriovenous fistula of the kidney. Dramatic relief of the cardiac failure, as well as of the hypertension following corrective surgical procedures, is equally characteristic.

The blood pressure, which was recorded in 12 of the 15 cases reviewed, was elevated in 11. Preoperative and postoperative blood pressures were recorded in 9 cases, and in all but 1 the elevated pressure returned to normal after operation.

The size of the heart was recorded in 12 of the patients, and of these 11 had cardiac enlargement. Lowered reserve or heart failure was present in 12 of the 15 patients. The cardiac symptoms were relieved in every patient whose fistula was removed.

In 6 cases the size of the heart was recorded both before and after operation. In 5 the heart regained its normal dimensions, and in 1 it returned to almost normal size.

In most cases the hypertension was associated with typical hypertensive changes in the retina, and in 1, the retinopathy was of the group 4 category.[3] A complete return of the ocular fundi to normal followed nephrectomy in every case.

The bruits associated with these arteriovenous fistulas have the classic auscultatory features of fistulas in other parts of the body but differ somewhat in being widespread and diffuse and not sharply localized. A thrill is commonly palpable. So far as is known now, an easily detectable bruit is present in all such arteriovenous fistulas.

Pain low in the abdomen was an occasional symptom, and gross hematuria was the presenting symptom in 3 cases.

The urine may be normal, or it may contain considerable albumin, casts, and erythrocytes. Except for the first patient whose case is recorded in the literature none of the patients had a tendency to elevated blood urea; the 1 exception was in terminal condition at the time of diagnosis.

Diagnostic Procedures

Excretory urograms were made for 12 of the 15 patients and showed abnormalities in 11. In the twelfth case that was reported by Kirby and associates,[11] the urogram showed nothing abnormal.

The first instance in which the diagnosis was confirmed and the lesion was demonstrated without the benefit of operation or postmortem examination did not occur until 1954 when an aortogram demonstrated the presence of the lesion (our case 1). In the last 7 cases,[4, 11, 14, 15] including our cases, an aortogram or angiogram has demonstrated the arteriovenous fistulas described.

Special catheterization procedures were carried out in 3 instances. The demonstration of arterialization of the inferior vena cava blood, and particularly of arterial blood from the renal vein, should be considered diagnostic. A marked reduction in the recircula

tion time as shown by the indicator-dilution test is characteristic of arteriovenous shunts. Increased cardiac output should be demonstrable.

The indicator-dilution curves in arteriovenous fistulas of the kidney were studied recently by Fox and Wood.[17] Preoperative and postoperative curves shown in figure 7 are part of the catheterization study done in our case 1.

Pathophysiologic Features

The overloading of the circulation because of high cardiac output is characteristic of arteriovenous fistulas from the renal as well as from the peripheral vessels. The blood volume is increased. The pulse pressure becomes widened through lowering of the diastolic pressure in peripheral arteriovenous fistulas and through increase in systolic pressure and a relative lowering of the diastolic pressure in arteriovenous fistulas of the kidney (table 2).

The degree of alteration of the circulatory dynamics is proportioned to the size of the fistula, the gradient of pressure, and the length of time the fistula has been present. The factor of size is demonstrated by a patient who had a large fistula between the abdominal aorta and the inferior vena cava. Only 3 weeks elapsed between the trauma that caused the fistula and the development of severe intractable heart failure.

There are several reasons for the commonly noted cardiac enlargement and heart failure in cases of renal arteriovenous fistulas. The pressure as well as the pulsatile character of the arterial blood in the renal artery distal to the fistula is decreased and with it the rate of flow to the kidney.[18] This gives an effect similar to that seen in a Goldblatt kidney, and hypertension almost invariably results. An atrophic renal cortex is characteristic, and, at times, has been associated with hydronephrosis.

With the development of hypertension, the pressure gradient across the fistula is increased, and a vicious cycle is established. The hypertension augments the flow through the fistula, which tends to cause further increase

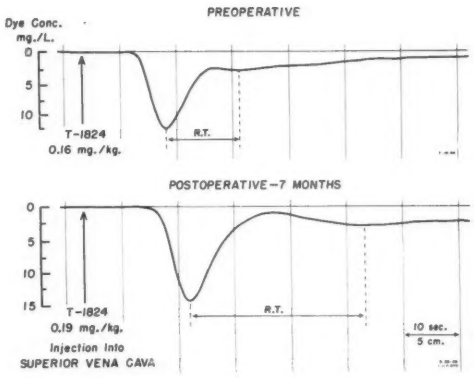

Fig. 7. Case 1. Dilution curves recorded at the radial artery before and after repair of an arteriovenous fistula of the right renal vessels.

in the cardiac output. The latter, in turn, presents more blood at increasing pressures to the fistulous tract.

Of great significance in illustrating the importance of the renal factor in the production of hypertension, cardiac enlargement, and heart failure is the return of the blood pressure and the size of the heart to normal in almost every case following surgical removal of the kidney along with the fistulous tract.

Summary

Only 5 reports of cases of renal arteriovenous fistula appeared before or in 1953. Subsequently, 7 isolated reports brought the total to 12, and the 3 that we are reporting make 15.

In reviewing the subject, the classification, incidence, causation, clinical features, diagnostic procedures, and pathophysiologic features were considered. Good evidence supports the thesis that in cases of congenital arteriovenous fistula an eroding renal arterial aneurysm is etiologic.

Outstanding clinical features were hypertension (to group 4) and myocardial insufficiency; these contrast markedly with features of the usual peripheral arteriovenous fistula. Dramatic relief of heart failure and lowered reserve followed corrective operation in every case in which these features were recorded; relief of hypertension followed corrective operation in 11 of 12 cases in which

this feature was mentioned. A loud, diffuse, continuous bruit invariably was present.

Preoperative and postoperative catheterization and indicator-dilution studies, angiograms and aortograms are diagnostic measures emphasized in our 3 cases. Arterialization of blood in the vena cava, greatly increased cardiac output, and markedly shortened recirculation times of the dye were found. Excretory urograms were abnormal in 11 of the 12 cases in which they were made.

The mechanism producing hypertension appears related to loss of pressure, decrease in flow, and loss of pulsatile character in the renal artery distal to the fistula, giving a Goldblatt-kidney type of end result. A vicious cycle of increasing hypertension followed by increasing flow through the shunt makes heart failure inevitable.

Since 10 of the 15 cases were reported in the last 4 years, indicating that the lesion is commoner than previously supposed, we advise auscultation over the renal regions in patients with cardiac enlargement or failure of unknown causation, unexplained deformities in urograms, and renal tumors.

Summario in Interlingua

Solmente 5 reportos de arterio-venose fistula renal esseva publicate ante o in 1953. Subsequentemente, reportos isolate augmentava le total a 12. Le 3 casos del presente reporto completa un total de 15.

Es presentate un revista del thema, incluse le classification, le incidentia, le causation, le characteristicas clinic, le technicas diagnostic, e le aspectos pathophysiologic. Il existe forte indicationes in supporto del these que in casos de congenite fistula arterio-venose, un erodente aneyrysma reno-arterial es le factor etiologic.

Eminente aspectos clinic esseva hypertension (a gruppo 4) e insufficientia myocardial. Istos contrasta marcatemente con aspectos del usual fistulas arteriovenose peripheric. Un dramatic alleviamento del disfallimento cardiac e del reducite reserva sequeva le chirurgia corrective in omne casos in que le mentionate aspectos esseva presente. Alleviamento del hypertension sequeva le chirurgia corrective in 11 del 12 casos in que iste aspecto esseva mentionate. Un forte, diffuse, e continue ruito esseva presente in omne casos.

Studios de catheterismo pre- e postoperatori e studios a dilution de indicatores si ben como angiogrammas e aortogrammas es mesuras diagnostic de importantia sublineate in nostre 3 casos. Esseva constatate arterialisation del sanguine in le vena cave, marcate augmentos del rendimento cardiac, e multo reducite tempores de recirculation del tinctura indicatori. Urogrammas excretori esseva anormal in 11 del 12 casos in que illos esseva effectuate.

Le mechanismo que produce le hypertension pare esser relationate a perdita de tension, reduction de fluxo, e perdita de character pulsatil in le arteria renal distal al fistula, resultante in un effecto termin 1 del typo de ren de Goldblatt. Un circulo vitiose de crescente hypertension sequite per un fluxo crescente via le derivation rende le supervenientia de disfallimento cardiac satis inevitabile.

Viste que 10 del 15 casos esseva reportate in le passate 4 annos, lo que indica que le lesion es plus commun que previemente supponite, nos recommenda auscultation supra le regiones renal in patientes con allargamento o disfallimento cardiac de etiologia obscur, con non-explicate deformitates del urogramma, e con tumores renal.

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I think this truth must needs follow and be apparent to all men.

1. First, That the blood is continually, and without any intermission, transmitted out of the vena cava into the arteries, in so great abundance, that it cannot be recruited by those things we take in, and insomuch that the whole mass of blood would quickly pass through.
2. In the second place, that continually, duly, and without cease, the blood is driven into every member and part, and enters by the pulse of the arteries and that in far greater abundance than is necessary for nourishment, or than the whole mass is able to furnish.
3. And likewise thirdly, that the veins themselves do perpetually bring back this blood into the mansion of the heart.

These things being prov'd, I think it will appear that it doth go round, is returned, thrust forward, and comes back from the heart into the extremities, and from thence into the heart again, and so makes as it were a circular motion.—William Harvey. *De Motu Cordis*, 1628.

Acute Reversible Heart Failure in Severe Iron-Deficiency Anemia Associated with Hookworm Infestation in Uganda Africans

By K. Somers, M.B., B.Ch. (W'Rand), M.R.C.P., D.C.H.

Severe iron deficiency anemia is a common sequel to the heavy hookworm infestations prevalent in Uganda, and in some hypoxia can be so severe that heart failure supervenes. The clinical manifestations in 15 cases are described. Comment is made on reversible electrocardiographic changes.

SEVERE iron-deficiency anemia associated with hookworm infestation is common in Uganda and during the year 1957, accounted for 114 or 5 per cent of all adult medical admissions, excluding pediatrics, into Mulago Hospital.[1]

It is not intended in this communication to enter into the controversy over the role of the hookworm in the causation of the anemia,[2-5] but it can be stated at the outset that experience at Mulago Hospital continues to confirm Lehmann's findings[6, 7] that iron alone will not cure the anemia and that, in addition, removal of the hookworms will result in a rapid improvement.

Severe anemia from any cause may affect the heart by producing a hyperkinetic circulatory state with its manifestations of tachycardia, dyspnea, and edema.[8] These are commonplace findings in severe anemia associated with hookworm infestation seen at Mulago. Furthermore, congestive failure due to the anemia is not uncommonly seen and this report is concerned with a study of heart failure in patients with severe anemia associated with heavy hookworm infestation.

Material and Methods

Diagnosis. It is difficult clinically to recognize congestive failure in severe anemia for the usual signs may have other interpretations. Thus, a raised venous pressure may be part of the physiologic mechanism maintaining a high cardiac output as shown by McMichael,[9] and edema is common in uncomplicated anemia. Failure can only be diagnosed on a careful consideration of these signs as well as orthopnea, paroxysmal cardiac dyspnea and pulmonary edema, enlargement and tenderness of the liver, and gross cardiac enlargement with diastolic gallop rhythm.

In the cases selected for study, a diagnosis of anemia associated with hookworm infestation was arrived at only where severe iron-deficiency anemia was associated with evidence of occult blood and hookworm ova in the stool and by the exclusion of other possible causes of anemia, e.g., esophageal varices associated with portal hypertension, malaria, and sickle-cell disease, all commonly encountered conditions in Uganda. Trowell's dictum[10] that the diagnosis of hookworm anemia can be absolute only in retrospect when the patient is discharged, fit and cured, was always borne in mind.

At physical examination, a careful note was made of findings in the cardiovascular system, and a total of 15 cases (table 1) were selected in whom there was no doubt about the presence of congestive failure and in whom no other concomitant cause for heart failure could be discovered. In each case with failure an x-ray of the chest and an electrocardiogram were taken before and after treatment. Hemoglobin levels were estimated weekly throughout stay in hospital.

Treatment. Treatment consisted of oral and intramuscular iron ("Imferron"), transfusions in severely ill cases if blood was available, and digoxin in desperate cases of failure. A low-salt ward diet was prescribed and patients were dewormed with tetrachlorethylene at hemoglobin levels of 45 per cent (6.3 Gm./100 ml.) or over. A single dose was sufficient but in 3 cases (cases 6, 10, and 12) a second dose was necessary because of the persisting worm load as judged from the continued presence of ova in the stools.

Observations. Of the 15 cases studied, 10 were male and 5 female, which roughly reflects the ratio of intake at Mulago Hospital. Their mean estimated age was 26.3 years with a range of 5 to 50 years. The patient

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belonged to various tribal groups found in Kampala. Six were Ganda and 5 of the Ruanda-Urundi group.

An attempt to assess the duration of anemia had to be given up because the information obtained was unreliable. More accurate accounts of the duration of heart failure were noted when a definite immediate history of orthopnea, paroxysmal cardiac dyspnea, or spontaneous pain in the right hypochondrium due to hepatic distention was obtainable. On such estimates the duration of failure averaged 4.7 weeks, with a range of 1 to 8 weeks. None of the patients complained of symptoms of angina, which is perhaps analogous to the absence of coronary disease in the African in Uganda. Palpitations with discomfort in the left chest were, however, common complaints.

All the patients had systolic murmurs over the left sternal border or at the apex which either improved or disappeared after treatment. No diastolic murmurs were heard in any of the series. A diastolic gallop was heard in nearly all cases.

Investigations. The hemoglobin on admission averaged 19 per cent (2.7 Gm./100 ml.) and ranged from 8.1 to 33.3 per cent (1.1 Gm. to 4.6 Gm./100 ml.). Of the 12 cases whose electrocardiograms were taken, 9 showed abnormalities that reverted to normal after treatment. All the cases showed radiologic evidence of generalized enlargement of the heart and the reduction in size after treatment in case 6 is shown in figure 1. Two cases had pulmonary atelectasis followed by complete reexpansion in one (case 6) and recurrent pneumonia in the other (case 10) but in neither was it felt that atelectasis or infection contributed to the heart failure.

TABLE 1.—*Clinical Data in Five Cases*

Case no.	Sex	Age	Duration of chronic congestive failure (wks.)	Hemoglobin on admission % (Gm.)	Electrocardiographic changes	Result
1	M	40	4	14 (2.0)	+	Cure
2	F	22	?	26 (3.6)	—	Death
3	M	26	8	11 (1.5)	+	Cure
4	F	50	4	—15*	NT	Death
5	F	24	6	27 (3.8)	+	Death
6	M	10	3	33 (4.6)	+	Cure
7	M	36	8	13 (1.8)	+	Death
8	M	5	4	14 (2.0)	+	Cure
9	F	40	4	21 (2.9)	—	Absconded
10	M	30	8	15 (2.1)	+	Cure
11	M	7	1	15 (2.1)	—	Cure
12	M	45	4	29 (4.1)	+	Cure
13	M	30	?	16 (2.2)	NT	Cure
14	F	22	?	26 (3.6)	NT	Death
15	M	7	2	8 (1.1)	+	Absconded

*Clinical estimate.
NT = not taken.

Necropsy Findings. Of the 5 deaths, 4 were preceded by sudden collapse within a few hours of admission. Three were examined

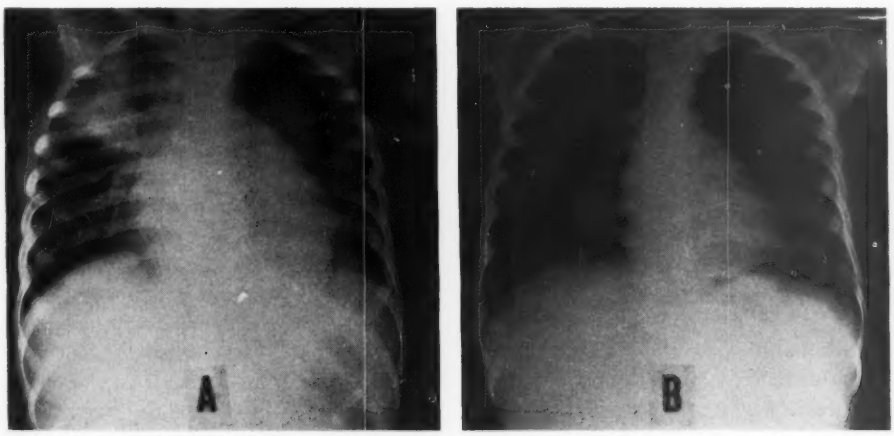

FIG. 1. Skiagrams showing general cardiac enlargement in cases 6 and 8. *A.* Before treatment; collapsed right upper lobe. *B.* After treatment of anemia.

postmortem and in each case necropsy revealed a hookworm count of more than a thousand. All the internal organs showed marked pallor. The chambers of the heart, especially the left ventricle, were dilated and the heart muscle in 2 cases (cases 14 and 15) showed thrush-breast streaking. No coexistent cardiac lesions or evidence of endomyocardial fibrosis, a common cause of heart failure described from Uganda,[11, 12, 31] was detected in any case. Pulmonary edema was noted in all the cases examined.

Discussion

Heart failure due to anemia is rare in Western communities, and Porter and James[14] go so far as to state that if failure does occur in an anemic patient, the coexistence of an intrinsic cardiovascular disease is almost certain. In the East however, chronic severe anemia is known to be a not uncommon cause of heart failure.[15, 16] Likewise in Africa, Beet[17] has noted the frequent complication of heart failure in anemia occurring in Nigeria. In the study by Sanghvi et al.[16] in India of 60 cases of severe anemia due to various causes, 20 were complicated by heart failure. In the majority the anemia was ascribed either to chronic malaria or hookworm infestation. In the Mulago series, evidence in favor of hookworm as the sole causative factor has been overwhelming, and malaria seems unimportant in the development of the anemia.

It is interesting to speculate why only a small number of our severely anemic patients develop heart failure. The answer lies perhaps with the chronicity rather than the severity of the anemia, an impression that seems logical in the knowledge that nutritional degenerative changes may occur in the cardiac muscle as a result of chronic hypoxia, reducing its reserve and predisposing to heart failure. If retrospective histories of weakness and tiredness could be relied upon to suggest the duration of anemia, what is now only a clinical impression might be confirmed further. In practice, however, the interrogation for such symptoms proved worthless and had to be abandoned.

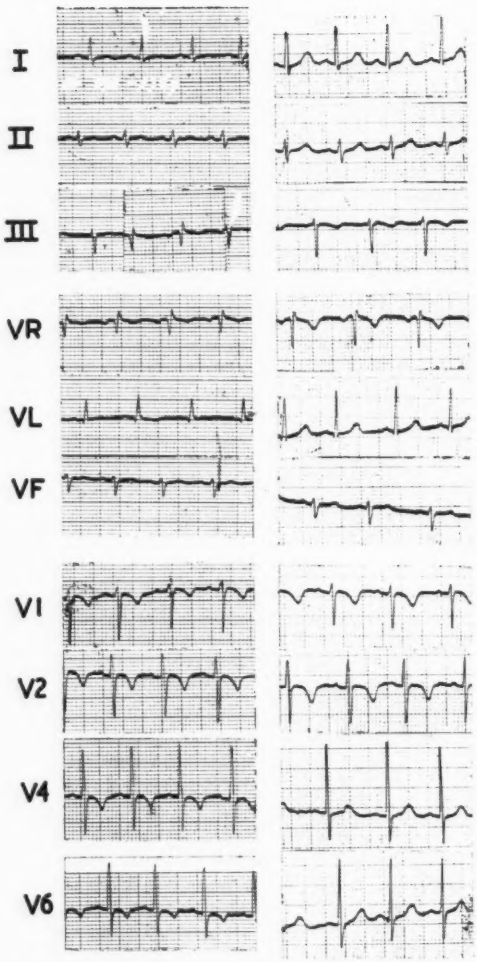

Fig. 2. Electrocardiograms of case 3 showing low voltage and flat or inverted T wave in all leads before treatment and improvement after correction of anemia.

The factors of malnutrition and thiamine deficiency might be suggested as possible factors in the causation of heart failure in these cases. In our hookworm series, however, treatment with adequate diet, iron and vitamins alone will not cure. Moreover, the syndromes of nutritional heart disease[18] and those amenable to thiamine,[19] described from South Africa, are different in that anemia is not a striking feature of the illness.

Sanghvi et al.[16] noted electrocardiographic changes in all their cases of severe anemia

with heart failure. In the series presented here, 12 had cardiograms taken, of whom 9 showed unequivocal abnormalities. The faults shown consisted of low voltage, depressed S-T segments, or flat or inverted T waves in left ventricular surface leads or their equivalents. As the anemia improved under treatment, these faults, as classically observed,[20] were also corrected (fig. 2).

The high mortality figure is alarming. Characteristically, death was preceded by a sudden unexpected collapse for which no cause could be found at necropsy. Doubtless, most of these cases might have been saved by early blood transfusions, if blood was available immediately, and whenever possible it is now our policy to treat with packed-cell transfusions whenever compatible blood is available. It is not generally easy to obtain donor blood in Kampala.

The finding of hookworm loads in excess of 1,000 at necropsy and Tasker's findings[4] of a blood loss of 0.1 ml. of blood per worm per day makes the problem of hookworm disease in general more important than its cardiovascular effects suggest.

I am indebted to Dr. Grusin[19] for the description "acute reversible heart failure in Africans" which I have borrowed for the title of this paper because it brings to mind the essentially preventable and curable aspects of another cause of heart failure in Africa.

Summary

Fifteen cases of acute reversible heart failure associated with severe hookworm anemia have been studied. Clinical signs are discussed with special reference to the diagnosis of cardiac failure and reversible electrocardiographic abnormalities before and after treatment.

Acknowledgment

I would like to thank Professor A. W. Williams and Dr. P. W. Hutton for encouragement and advice, and the Director of Medical Services, Uganda, for facilities at Mulago Hospital.

Summario in Interlingua

Esseva studiate 15 casos de acute reversibile disfallimento cardiac, associate con sever anemia per strongylidas. Le signos clinic es discutite con referentia particular al diagnose de disfallimento cardiac e al reversibile anormalitates electrocardiographic ante e post le tractamento.

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Studies of Blood Coagulation and Fibrinolysis in Patients with Idiopathic Hyperlipemia and Primary Hypercholesteremia before and after a Fatty Meal

By Saul I. Nitzberg, M.D., M. Anthony Peyman, D.M., M.R.C.P., Robert Goldstein, M.D., and Samuel Proger, M.D.

In view of the current interest in the possible relationship between elevated serum lipid levels, increased coagulability of the blood (or decreased blood fibrinolysis) and ischemic heart disease, the clotting and fibrinolytic activity of the blood were studied before and after a fatty meal in 9 patients with idiopathic hyperlipemia, 10 patients with primary hypercholesteremia, and 10 normal subjects. Six patients had evidence of coronary heart disease. The methods of study included procedures designed to assess the over-all coagulability of the blood as well as the measurement of specific clotting factors. Blood fibrinolytic activity was measured by both direct and indirect methods. Serum lipid studies were performed simultaneously.

DURING recent years, increasing attention has been paid to the role of the serum lipids in the development of atherosclerosis with particular reference to coronary atherosclerosis. There has also been much discussion concerning the possible significance of the state of coagulability of the blood in the pathogenesis of coronary atherosclerosis since the suggestion by Duguid[1, 2] that atherosclerotic plaques may be derived from mural fibrin thrombi. Indeed, it has even been postulated that intravascular coagulation is a constant process and that small fibrin strands are being continuously deposited on the vascular endothelium only to be removed by the naturally occurring process of fibrinolysis.[3, 4] According to this concept, any shift in such a delicate equilibrium toward either an increase in blood clotting activity or a decrease in blood fibrinolytic activity would allow excessive deposition of fibrin even to the extent of causing complete vascular occlusion. Some workers[5, 6] have contended that *hyperlipemia* may disturb this balance, leading not only to acceleration of blood clotting but also to retardation of blood fibrinolysis. Most of the previous reports in this field, however, have been based upon evaluation of the clotting and fibrinolytic activity of the blood either after the ingestion of a fatty meal in normal subjects or after the addition of fat to plasma in vitro.[7–14] So far only a single report is available regarding blood coagulation activity in patients with abnormal lipid metabolism in whom hyperlipemia or hypercholesteremia, or both, exist as part of an inherent disease process.[15] In these patients a high blood lipid level is present even in the fasting state.

It was therefore decided to study the clotting and fibrinolytic activity of the blood in a selected group of patients with idiopathic hyperlipemia and primary hypercholesteremia (including those with familial xanthomatosis) before and after a fatty meal. Moreover, investigation of these patients seemed of additional interest, since many of them develop widespread atherosclerosis and early coronary disease. Observations on this unique group of patients might be of value in defining the relationship between elevated serum lipid levels (i.e., hyperlipemia or hypercholesteremia), increased coagulability of the blood (or decreased blood fibrinolysis), and ischemic heart disease.

Material and Methods

The subjects were divided into 3 groups. The first group consisted of 9 patients with idiopathic

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hyperlipemia, a disorder of fat metabolism, usually familial, characterized by lactescent serum and high concentrations of triglycerides in the fasting state, with or without high serum cholesterol and phospholipid levels. There were 7 males and 2 females in this group, ranging in age from 25 to 55 years. Cases 1, 3, and 9 had extensive xanthomatous lesions. Cases 1, 3, and 5 had clinical and electrocardiographic evidence of ischemic heart disease, amounting in case 1 to acute coronary heart disease without major infarction.

The second group was composed of 10 patients with primary hypercholesteremia, a disorder of fat metabolism, frequently familial, characterized by clear serum with high concentrations of cholesterol in the fasting state. There is usually a concomitant elevation of the serum phospholipid levels. None of the patients in this series showed evidence of diabetes mellitus, nephrosis, or myxedema. There were 5 males and 5 females in the hypercholesteremic group, ranging in age from 27 to 61 years. Cases 10, 11, 13, 17, and 18 had extensive xanthomatous lesions. Cases 10, 17, and 18 had clinical and electrocardiographic evidence of ischemic heart disease amounting in cases 10 and 17 to acute coronary heart disease without major infarction.

Ten normal control subjects comprised the third group (8 males and 2 females, ages 19 to 39). The subjects in this group were chosen for the following reasons: (1) relative youth, (2) clear fasting serum with normal triglyceride and cholesterol levels, (3) absence of xanthomatous lesions, (4) no evidence of ischemic heart disease.

The subjects were instructed to fast after 10:00 p.m. and blood was drawn at 9:00 a.m. on the following morning. They were then given a meal consisting of 2 eggs, 3 strips of bacon, 2 pats of butter, and 4 ounces of 20 per cent cream along with toast, cereal, and coffee; this meal contained 85 Gm. of fat. All subjects were supervised during the breakfast to ensure that the entire meal was consumed. Postprandial blood specimens were obtained 4 hours after ingestion of the meal during the maximal lipemic effects.[16] Blood was withdrawn by clean venipuncture with a 19-gage siliconized needle with use of the 2-syringe technic. Blood obtained in the first syringe was used for the determination of the serum lipids. The subsequent blood drawn into a chilled 30-ml. siliconized syringe and a stop watch was started as soon as the blood entered the syringe. Subsequently 1.5 ml. of blood was withdrawn through the same needle into a calibrated siliconized tuberculin syringe for thrombelastography, a separate stop watch being started as soon as blood entered the syringe. While a technician was emptying the blood from the large silicone syringe into the appropriate test tubes, one of the workers immediately placed 0.35 ml. of the blood from the tuberculin syringe into each of the 3 cuvettes of the thrombelastograph. The blood from the large silicone syringe was distributed as follows: (a) 1.0 ml. into each of 6 siliconized test tubes for the whole blood clotting time, (b) 9.0 ml. into a chilled plastic tube containing 1.0 ml. of 2.5 per cent sodium citrate for spinning in the refrigerated centrifuge for 30 minutes at 4,000 r.p.m. to obtain platelet-poor plasma, (c) 4.5 ml. into each of 3 plain glass tubes containing 0.5 ml. of 0.1 M sodium oxalate for centrifuging at 1,500 r.p.m. for 10 minutes to obtain platelet-rich plasma.

Coagulation Methods

The prothrombin concentration of plasma was determined by the modified method of Owren as described by Alexander.[17] A saline extract of acetone-dried human brain was used as the source of thromboplastin. *Factor V (labile factor) activity* was measured by determining the corrective effect on the prothrombin time of aged plasma (The substrate had normal values for prothrombin, factor VII, and fibrinogen.) *Factor VII (S.P.C.A.) activity* was measured by a modification of the Owren procedure.[18] *The plasma fibrinogen level* was determined by the method of Ratnoff and Menzie as modified by Holburn.[19] The normal fasting levels were between 200 and 400 mg. per 100 ml. of plasma. *The coagulation time of recalcified plasma* was performed on platelet-rich plasma and platelet-poor plasma: 0.1 ml. of 0.9 per cent saline and 0.1 ml. of 0.02 M calcium chloride were added to 0.1 ml. of the respective plasmas and the clotting times were estimated in duplicate. The normal fasting values for the platelet-rich plasmas were between 75-105 seconds and for the platelet-poor plasmas were greater than 2 minutes. The error between duplicate samples was ± 15 seconds (platelet-rich plasma) and ± 30 seconds (platelet-poor plasma). *The whole blood clotting time in silicone glassware (Lee and White method as modified by Merskey)*[20] was recorded as the mean of the clotting time in 6 tubes (13 × 100 mm.). The normal fasting values for this test were 20 to 40 minutes. *The prothrombin consumption* of plasma and serum was determined as mentioned above. Serum for this test was obtained by recalcifying 0.5 ml. of platelet-poor plasma with 0.1 ml. of 0.1 M calcium chloride. At the end of 1 hour 0.1 ml. of 3.8 per cent sodium citrate was added and the serum was separated. The normal fasting values for this test were 30 to 75 per cent. *The heparin tolerance test* was performed as described by Soulier and Le Bolloch.[21] The end-point in the fourth tube was used for comparison of the clotting ability of the fasting and postprandial

plasmas in the presence of heparin. The normal fasting clotting time in the fourth tube ranged between 10 and 14.5 minutes. *Thrombelastography.* A Hellige thrombelastogram was employed, determinations being performed on whole blood according to the method of Hartert.[22] The 3 components of the thrombelastogram that reflect the coagulability of the blood are 1. "R" (reaction time) indicating the period from the entry of blood into the syringe to the initial formation of fibrin in the cuvette. The normal fasting values were between 9.0 and 11.5 minutes. 2. "K" indicating the interval from the end of "R" to the end-point of the clot formation. The normal fasting values were 5.0 to 6.75 minutes. 3. "MA" (maximal amplitude) measuring the elasticity of the clot. The normal fasting values were between 46 and 50 mm. Shortened "R" and "K" values and lengthened "MA" values indicate increased coagulability of the blood. *The thromboplastin generation test* as originally modified by Hicks and Pitney[23] was further modified as follows: 1. Platelet-poor plasma was used. 2. Inosithin was diluted in saline in a concentration of 0.5 mg./ml. to determine the potency of this thromboplastic material. 3. The test was repeated by further diluting the previously prepared Inosithin to 1 in 150 of veronal-buffer-isotonic saline mixture at pH 7.4. Clotting times were determined at 1-minute intervals for 15 minutes. With normal fasting plasma, clotting times of 8 to 10 seconds were obtained after 10 minutes of incubation. The Inosithin was diluted in order to increase the sensitivity of the test. 4. The thromboplastin generation test was also determined without the addition of any foreign thromboplastic material in order to detect thromboplastic activity in the plasma were such present. Clotting times were determined at 5-minute intervals for 30 minutes. Fasting clotting times ranging between 20 and 50 seconds were obtained after 15 to 25 minutes of incubation. This procedure was performed at 37 C. *The 1-stage* prothrombin time (Quick's method).[24] A saline extract of acetone dried human brain was used as the source of thromboplastin. The normal fasting values were between 12 and 14 seconds. *The Stypven time (Russell viper venom test).* Russell viper venom (Stypven) was diluted 1 in 10,000 with 0.9 per cent saline; 0.1 ml. of platelet-poor plasma diluted 1:2 with 0.9 per cent saline was incubated at 37 C. with 0.1 ml. of the previously prepared Stypven, and after 1 minute 0.1 ml. of 0.02 M calcium chloride was added, and the clotting time was determined in duplicate. All determinations were performed immediately after the plasma was obtained. The normal fasting values were between 20 and 30 seconds.

Fibrinolysis Methods

Two methods were employed. *Method 1* measured the fibrinolytic activity of blood as described by Fearnley et al.[25] *Method 2* measured the profibrinolysin activity of plasma. A modification of the method described by Loomis[26] was used: 0.1 ml. of bovine thrombin (Upjohn) containing 50 units per ml. and 0.5 ml. of citrated platelet-poor plasma were added in rapid succession to 0.1 ml of Varidase (Lederle Laboratories) containing 2,000 units of streptokinase per ml. and the resulting mixture was incubated at 37 C. Ten seconds after the reagents had been thoroughly mixed, at which time a clot had already formed, an open-ended capillary tube was inserted perpendicularly into the bottom of the clot. The tube was left undisturbed in a glass water bath at 37 C. Once fibrinolysis had begun, the liquefied plasma ascended into the capillary tube. The end-point was taken at the instant that the liquid level in the capillary tube reached the upper surface of the clot. Normal fasting values ranged between 60 and 80 seconds.

The 2 methods employed in the estimation of fibrinolytic activity of the fasting and postprandial plasma differed not only in their technic but also in that they measured separate phases of the fibrinolytic process. The lysis time as measured by the Fearnley technic (method 1) essentially reflects the concentration of free or active fibrinolysin in freshly shed blood. Method 2 does not measure fibrinolysis directly but rather expresses the concentration of the precursor of fibrinolysin present in the plasma which, in the presence of streptokinase, becomes converted to fibrinolysin. This activated lysin is independent of the free fibrinolysin normally present in the plasma inasmuch as the latter type is neutralized, upon standing, by the plasma antifibrinolysin. It is evident, therefore, with method 1 a longer fibrinolysis time following the fatty meal is indicative of inhibition of fibrinolysis, whereas a shorter fibrinolysis time signifies that fibrinolysis has become accelerated postprandially. The interpretation of results is more difficult when method 2 is used and the following scheme is presented for clarification of the problem.

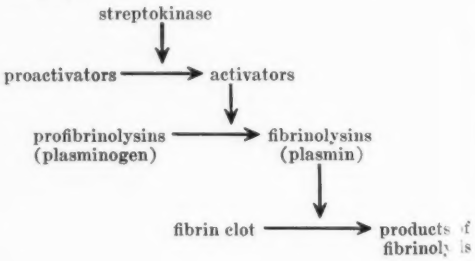

TABLE 1.—*Fasting and Postprandial Values of Silicone Clotting Time, Thrombelastography, Heparin Tolerance, and Prothrombin Consumption*

Case no.	Age	Sex	Silicone clotting time (min.)		Thrombelastography* R Min.		Thrombelastography* K Min.		Heparin tolerance (min.)		Prothrombin consumption (%)	
			F	PP	F	PP	F	PP	F	PP	F	PP
Patients with idiopathic hyperlipemia												
1	37	M	24	23.5	11.4	11.5	6.75	7.9	10.5	15	62	68
2	45	M	30	23	—	—	—	—	10	8	—	—
3	47	F	24	23.5	9.2	8.7	5.2	5.3	10	9.5	62	67
4	25	M	36	31	10.4	10.4	6.0	5.25	10	9.5	74	37
5	55	F	42.5	29	11.5	11.25	5.6	5.0	15	12	69	75
6	40	M	30	29	10.2	10.25	6.3	5.75	9.5	8.5	77	73
7	32	M	23	25	9.25	9.2	5.1	5.25	12	11.5	73	67
8	38	M	27.5	27.5	11.5	9.9	5.2	4.75	10.5	9.5	44	37
9	44	M	22	25.5	11.25	10.7	5.5	5.25	8	13.5	73	59
Patients with primary hypercholesteremia												
10	27	F	60	32	10.75	10.3	5.0	5.0	12	11.5	68	54
11	35	F	31	34	9.8	9.75	5.2	5.0	12	15	74	64
12	47	F	24	27	9.6	9.5	5.75	4.5	15	12.5	48	33
13	45	M	24	41	9.9	8.7	5.25	4.9	8.5	8.5	96	75
14	50	M	29	28	10.25	9.5	4.9	5.1	12.5	12	61	41
15	31	M	29	22	11.0	10.75	6.9	6.5	11	14	66	46
16	54	F	27	23	10.25	5.4	5.4	5.25	15	12	49	60
17	37	F	40	35.5	10.5	6.8	6.8	7.1	11	9.5	82	65
18	29	M	21	24	9.8	5.2	5.2	5.25	15	15.5	44	57
19	61	M	21	19.5	9.4	6.5	6.5	5.75	12.5	14	72	65
Normal controls												
20	28	F	24.5	25	10.3	9.25	5.2	5.0	14	13.5	47	47
21	33	M	27	29	9.75	9.0	6.1	6.0	11	10	53	62
22	32	M	21.5	22	9.2	8.7	6.1	6.2	13	12	57	72
23	34	M	28	26	10.5	9.8	6.0	5.7	12	10	71	70
24	29	M	26	37	10.75	10.5	5.8	6.1	12.5	12	57	66
25	32	M	29.5	30.5	10.8	11.1	6.25	6.1	13.5	10	45	51
26	30	F	22.5	23	11.25	10.75	6.5	6.3	10	10	48	33
27	33	M	24.5	30.5	11.25	11.0	6.75	6.1	8.5	7.5	72	60
28	39	M	31.5	41	11.25	9.5	6.1	6.8	14	13	31	42
29	19	M	24	25	9.25	9.30	5.7	5.8	13	10.5	36	61

*"MA" values were always between 46-50 mm.

F=fasting.

PP=postprandial.

Thus with this method prolongation of postprandial lysis could imply *one* of the following: 1. decrease in the level of pro-activators or profibrinolysins. 2. Inhibition of activation of pro-activators or inhibition of activation of fibrinolysins. 3. Inhibition of lysis of the fibrin clot. 4. An increase in plasma fibrinogen concentration. The error between duplicate samples was considered to be ± 20 minutes with method 1 and ± 5 seconds with method 2. The degree of significant alteration in the postprandial fibrinolysis time could not be established with certainty using method 1, since the individual variability in the fasting state was very marked (i.e., between 3 and 13 hours). With method 2, the significant alteration in the fibrinolysis time following the fatty meal was taken to be ± 15 seconds.

CHEMICAL METHODS

The serum cholesterol and cholesterol esters were determined by the method of Schoenheimer and Sperry.[27] The *lipid phosphorus* was obtained by extracting the serum with Bloor's reagent and petroleum ether. The lipid phosphorus was converted to inorganic phosphorus by digestion and the inorganic phosphate so obtained was measured by the procedure of Fiske and SubbaRow.[28] A factor of 25 was used to convert the lipid phosphorus to phospholipids. *The total serum fatty acids* were determined by the method of Stoddard and Drury[29] and the *total serum lipids* by the gravimetric method as described by Peters and Van Slyke.[30] *The serum triglycerides* were not determined directly but were calculated by means of the following formula. Triglycerides

mg. per cent = fatty acids mg. per cent — 0.7 (cholesterol esters mg. per cent + phospholipids mg. per cent). *The serum beta lipoproteins* were determined by the nephelometric method of Bernfield et al.[31] *The serum turbidity* was determined by means of the Coleman Junior spectrophotometer at a wavelength of 620 mμ, with the instrument set to zero optical density with a clear normal serum sample.

Results

Blood Coagulation and Serum Lipid Data

The results of the coagulation studies in the 3 groups of subjects were divided into 2 main categories.

Category 1 was composed of the results of those tests that measure specific coagulation factors. These consisted of the prothrombin concentration of plasma, factor V (labile factor) activity, factor VII (S.P.C.A.) activity, and the plasma fibrinogen level. The values obtained for these factors were within normal limits in the fasting state and remained essentially unchanged after the fatty meal in the 3 groups of subjects.

Category 2 comprised the results of those procedures that measure the over-all coagulability of the blood (or plasma) with or without the addition of thromboplastic material. These consisted of the coagulation time of recalcified platelet rich and platelet poor plasma, the silicone clotting time of whole blood, the prothrombin consumption test, the heparin tolerance test, thrombelastography, the thromboplastin generation test, the 1-stage prothrombin time, and the Stypven time.

The results of the first 5 tests inclusive, performed without the addition of foreign thromboplastic material, were within normal limits in the fasting state and remained essentially unchanged after the fatty meal in the 3 groups of subjects (table 1).

The thromboplastin generation test gave essentially inconclusive results. In the fasting state, however, there appeared to be a tendency for the hyperlipemic and hypercholesteremic groups to develop a more potent thromboplastin. Thus 6 of the 9 patients with hyperlipemia and 6 of the 10 patients with hypercholesteremia showed clotting times between 20 and 35 seconds, whereas only 3 of the 10 normal subjects fell within this range. Postprandially there was even less difference between the normal subjects and the other 2 groups of patients.

The last 2 tests involve the use of thromboplastic material. The 1-stage prothrombin time, in which tissue thromboplastin was employed, constantly gave normal results in the 3 groups of subjects both before and after the fatty meal. On the other hand, the Stypven time, entailing the use of Russel viper venom as the thromboplastic agent, was the *one* coagulation test that almost always showed significant changes (i.e., acceleration) in the presence of hyperlipemia either in the fasting state (i.e., patients with idiopathic hyperlipemia) or following the fatty meal in all groups of subjects. For this reason the results of this test are considered in detail below.

As seen from table 2, the patients with idiopathic hyperlipemia were unique in that their fasting Stypven times were considerably shorter than those of the other 2 groups. On the other hand, the fasting Stypven times of the patients with primary hypercholesteremia fell within the normal range, even though they were slightly shorter than those of the control subjects. The degree of postprandial shortening of the Stypven time did not exceed 4 seconds in the hyperlipemic and hypercholesteremic groups, except for 1 patient in the former group (case 4) and 2 patients in the latter group (cases 12 and 18). In contrast, 7 of the 10 control subjects showed more than 4 seconds' shortening after the fatty meal. In an attempt to establish the postprandial variability of the Stypven response, tests were repeated on 3 additional days in 8 of the 10 normal subjects. Although the response of some of these subjects varied to a certain degree from day to day, in 70 per cent of instances there was still more than 4 seconds' postprandial shortening, a finding identical with the initial observations in this group. Thus it is clear that the change in the Stypven time following a fatty meal was more pronounced in the control subjects than in the patients with hypercholesteremia or hyper-

TABLE 2.—*Fasting and Postprandial Values of Stypven and Fibrinolysis Times in Relation to the Serum Lipid Changes*

Case no.	Age	Sex	Profibrinolysin: Stypven time (sec.) F	Stypven time (sec.) PP	Profibrinolysis time (sec.) F	Profibrinolysis time (sec.) PP	Serum lipids (mg. %): Total cholesterol F	Total cholesterol PP	Phospholipids F	Phospholipids PP	Fatty acids F	Fatty acids PP	Triglycerides F	Triglycerides PP	Total lipids F	Total lipids PP	Beta lipoproteins F	Beta lipoproteins PP	Serum turbidity F	Serum turbidity PP
Patients with idiopathic hyperlipemia (I.H.L.)																				
1	37	M	15.6	12.1	89	97	741	732	630	622	2378	2551	1564	1747	4220	4579	996.5	1002.0	.920	1.085
2	45	M	18.2	16.1	82	84	280	259	312	293	1125	1295	765	859	2347	2644	—	—	.686	.994
3	47	F	18.0	17.4	78	85	362	325	370	354	1496	1724	1049	1311	3433	3689	823.6	915.6	.484	.688
4	25	M	16.9	12.8	75	73	187	192	172	160	998	1224	784	1016	1962	2671	769.2	824.3	.426	.714
5	55	F	16.5	15.0	84	90	450	384	462	435	1546	1744	987	1238	3229	3743	902.4	1528.8	.502	.812
6	40	M	16.5	14.2	92	102	298	280	320	308	1342	1564	970	1210	2845	3334	745.7	829.2	.510	.845
7	32	M	15.6	12.5	69	75	255	240	260	273	739	890	427	577	1543	1724	895.2	1021.2	.456	.930
8	38	M	15.0	12.7	90	98	293	289	336	307	2041	2398	1729	2036	4526	4947	—	—	.878	1.280
9	44	M	10.8	9.5	93	99	708	724	530	554	2572	2733	1834	1976	5126	5372	1399.2	1435.2	.954	1.600
Patients with primary hypercholesteremia (P.H.)																				
10	27	F	24.4	24.0	72	74	440	428	346	322	657	779	199	341	1384	1749	—	—	.015	.357
11	35	F	23.7	23.0	67	71	440	417	406	363	634	675	126	211	1517	1730	1296.0	1442.4	.037	.288
12	47	F	29.7	22.8	76	80	405	405	427	368	621	651	124	196	1348	1524	1124.4	1172.4	.039	.302
13	45	M	18.0	17.5	63	73	379	390	284	330	528	605	139	183	1383	1525	907.2	1123.2	.118	.550
14	50	M	20.9	18.1	69	75	362	358	334	321	536	590	117	185	1142	1485	933.4	874.3	.073	.204
15	31	M	22.4	18.4	59	80	317	325	252	260	413	566	82	210	1183	1292	873.6	924.0	.119	.380
16	54	F	23.8	22.8	60	76	325	311	240	225	440	560	114	250	965	1000	823.2	831.6	.035	.255
17	37	F	25.8	24.2	67	74	453	440	422	403	705	784	188	287	1399	1424	694.3	714.0	.072	.350
18	29	M	18.2	11.5	79	58	476	445	343	322	690	830	210	378	1547	1676	1255.1	1324.4	—	—
19	61	M	23.7	22.2	65	70	325	289	328	278	639	689	251	353	1478	1645	844.8	937.2	.112	.450
Normal control subjects (N.C.)																				
20	28	F	27.9	20.1	68	70	158	160	174	163	335	354	134	160	758	765	621.6	596.4	.030	.196
21	33	M	25.8	16.4	75	77	198	198	210	215	286	528	39	278	724	1205	554.4	594.0	.075	.404
22	32	M	25.0	18.6	64	73	247	255	255	236	352	572	53	273	783	1430	721.2	792.0	.115	.417
23	34	M	26.6	20.5	71	79	142	136	125	130	184	276	26	117	508	694	568.8	591.6	.020	.160
24	29	M	23.8	23.6	64	71	217	214	230	236	299	436	32	166	770	933	602.4	649.2	.098	.441
25	32	M	26.2	20.0	78	60	217	214	210	227	404	643	147	380	820	1342	664.8	631.2	.124	.586
26	30	F	26.0	24.5	61	70	221	209	243	248	409	651	127	371	802	1250	544.8	526.8	.095	.288
27	33	M	20.8	17.5	67	83	202	188	210	203	364	552	116	316	704	1236	664.8	613.2	.049	.285
28	39	M	27.0	21.0	60	77	202	202	226	215	380	514	124	265	773	1342	544.8	709.4	.090	.201
29	19	M	26.3	16.5	73	74	154	154	145	138	336	489	156	314	760	1206	561.0	510.8	.129	.340

Fasting values

Groups	Stypven time (sec.) Range	Stypven time (sec.) Mean	Profibrinolysis lysis time (sec.) Range	Profibrinolysis lysis time (sec.) Mean
I.H.L.	10.8—18.2	15.9	69—93	83.5
P.H.	18.0—29.7	23.0	59—79	67.7
N.C.	20.8—27.9	25.5	60—78	68.1

F=Fasting.
PP=Postprandial.

pemia. The postprandial shortening of the Stypven time was essentially similar in the 2 abnormal groups even though the patients with hyperlipemia had such short Stypven times in the fasting state (table 2).

The invariably shortened Stypven times in the fasting state in the patients with idiopathic hyperlipemia would suggest a possible association with the lactescence of the serum or the elevated levels of triglycerides present in this group, factors not encountered in the other 2 groups. However, careful scrutiny of the results of individual patients in this group (table 2) failed to show a *strict* correlation in the majority of cases between the fasting Stypven times and the serum triglyceride levels. A similar lack of strict correlation between the fasting Stypven times and the serum triglycerides was also evident in the other 2 groups of subjects, although here again there was a general relationship. Following the fatty meal, it is clear (table 2) that every individual in the 3 groups showed some increase in the serum triglyceride levels and at the same time almost always developed a varying degree of shortening of the Stypven time. However, analysis of individual cases again failed to show a *strict* correlation between the postprandial changes in the Stypven time and the serum triglycerides.

The data also show that the fasting fatty acid levels were moderately or markedly elevated in 8 of the 10 patients with hypercholesteremia, while in the control subjects they were all within normal limits. These levels seemed to a certain degree to parallel the mean values of the fasting Stypven times in the respective groups of subjects. Following the fatty meal, an increase in the serum fatty acids, as with the serum triglycerides, was observed in all subjects. However, analysis of individual cases showed no *close* correlation between the postprandial changes in the serum fatty acids and those of the Stypven time.

During this study it became apparent that the Stypven time could to a certain extent be predicted by simple inspection of the serum. Thus a shortened Stypven time could be anticipated and was in fact always found in patients with idiopathic hyperlipemia who exhibited a lactescent serum in the fasting state, as well as usually in other subjects when their serum became turbid after a fatty meal. Similarly a clear serum was almost always associated with a Stypven time well within the normal range. These gross observations were further substantiated when the serum turbidity values were subsequently determined with the spectrophotometer. Although this general impression was essentially correct, analysis of individual cases, particularly in the postprandial state, failed to support the assumption that there was in fact a *strict* relationship between the turbidity of the serum and the length of the Stypven time.

Table 2 indicates that there was no correlation in the majority of cases between the fasting Stypven times and the serum cholesterol or phospholipid levels. The serum cholesterol values showed a slight increase in a few cases postprandially and remained unchanged or decreased slightly in the remainder. The serum phospholipid levels increased after the fatty meal in approximately one third of the total number of subjects. The shortening of the postprandial Stypven times was independent of these lipid changes.

There was no correlation between th Stypven time and the beta-lipoprotein level in any of the groups of subjects either in th fasting state or following the fatty meal.

Blood Fibrinolysis Data

Method 1. Determination of fibrinolyti activity by the Fearnley method.[25] There wa considerable individual variation in the fas ing fibrinolysis times (i.e., between 3 and 1 hours), although both the range of valu and the mean values of the fasting fibrinolysi times were essentially similar in the 3 group of subjects. Following the fatty meal ever subject in the series, with the exception of individual in each group, showed acceleratio of the fibrinolysis time to a greater or lesse extent, but again the 3 groups behaved alike.

Although this method has the advantage of measuring the fibrinolytic activity of freshly shed blood, it had certain limitations when employed in this series. Thus there were wide differences in the fasting fibrinolysis times among the different individuals. Furthermore, although there was a definite postprandial shortening of the fibrinolysis times in almost all individuals, it was difficult to assess the effect of the fatty meal inasmuch as these changes could have been the direct result of the fatty meal, or a reflection of the natural diurnal acceleration that was found by Fearnley et al.[25] to exist in normal subjects.

Method 2. Measurement of the profibrinolysin activity (streptokinase-induced fibrinolysis. The mean values of the fasting streptokinase-induced fibrinolysis times were almost identical in the normal and hypercholesteremic groups (i.e., 68.1 and 67.7 seconds respectively) but were noticeably different in the hyperlipemic group (i.e., 83.5 seconds) (table 2). In contrast to the results with the method employing spontaneous fibrinolysis (method 1) the majority of individuals exhibited some prolongation of the streptokinase-induced fibrinolysis times after the fatty meal. However, even with this method (method 2) the degree of postprandial p

lugation was considered to be of significance only 4 subjects, inasmuch as the limits of normal variability were taken to be ± 15 seconds. According to the same criteria 2 subjects showed significant shortening postprandially (table 2).

In an attempt to establish the variability of the fasting and postprandial fibrinolysis times in the same individuals, this method was employed on 3 additional consecutive days in 9 of the 10 normal subjects. These repeat studies gave closely similar results for the range and mean values (i.e., 61 to 77 and 68.0 seconds respectively) as compared with the original values in the fasting state (i.e., 60 to 78 and 68.1 seconds respectively). There was a variation in the postprandial response not exceeding ± 5 seconds in any one individual from day to day.

Regardless of the degree of inhibition of fibrinolysis by hyperlipemia, it is still uncertain at which stage the fat acts upon the various components of the fibrinolytic system. Since hyperlipemia was not associated with a change in fibrinogen levels, any effect upon the fibrinolytic system could have been a result of any of the other 3 mechanisms stated above.

The distinctly different fasting fibrinolysis times in the hyperlipemic group suggest a possible association with the high serum triglyceride levels, a feature not encountered in the normal and hypercholesteremic subjects. Moreover, the slight postprandial lengthening of the fibrinolysis time observed in the majority of individuals in this series was always accompanied by a rise in the serum triglyceride levels (table 2). However, although there appeared to be some association between the length of the fibrinolysis time and the level of serum triglycerides in the fasting state and postprandially in all groups, *no strict correlation* could in fact be found when individual cases were analyzed. Similar observations were made with regard to the fibrinolysis time and the serum turbidity in all groups of subjects. There was also some association between the fibrinolysis time and the serum fatty acids in the control and hyperlipemic groups, but this did not hold true for the hypercholesteremic group in which 8 of the 10 patients had slightly elevated fasting fatty acid levels and yet showed normal fibrinolysis times. There was no evidence in any individual of an association between the fibrinolysis time and the serum cholesterol or phospholipid levels either in the fasting state or postprandially. This is well exemplified by the results in the hypercholesteremic group, in which high serum cholesterol or phospholipid levels were accompanied by essentially normal fibrinolysis times in the fasting state. Finally, inspection of table 2 shows that there was no association between the fibrinolysis time and the beta-lipoprotein levels in any of the groups of subjects either before or after the fatty meal.

Discussion

The effect of hyperlipemia on blood coagulation is still the subject of much controversy. It is probable that the lack of uniformity of coagulation technics employed by various workers in this field is one reason for this difference of opinion, although in fact conflicting results have been reported even when identical methods have been used. Moreover, even if the serum lipids do exert some effect on coagulation, their actual mode of influence is still unknown. In this respect, some of the coagulation tests utilized in this series were those that are generally considered to reflect the over-all coagulability of the blood, while others were chosen because they are known to measure specific factors that participate in the various stages of coagulation. It is therefore of interest that almost all the coagulation tests employed in this study failed to provide any definite evidence of a constant trend toward increased coagulability of the blood either in the fasting state or after the ingestion of fat, even in those patients with idiopathic hyperlipemia or primary hypercholesteremia. One of these tests, the silicone clotting time, has been a particular source of disagreement. Thus a number of workers, including Waldron and Nichols,[7] Fullerton et al.,[8] O'Brien,[9] Buzina and Keys,[10] and

Mustard[11] contended on the basis of their experiments that alimentary hyperlipemia produces shortening of the whole blood clotting time in nonwettable glassware in normal subjects while others such as Tulloch et al.,[32] Merskey and Nossell,[20] although O'Brien[9] and Borrero et al.,[34] were unable to confirm these results. Another test essentially uninfluenced by alimentary hyperlipemia in this series was the coagulation time of recalcified plasma. This is in accord with the work of Merskey and Nossell,[20] although O'Brien[9] and Pilkington[35] using this test were able to demonstrate acceleration of coagulation following the feeding of fat to normal subjects. A technic which is being increasingly used in blood coagulation studies is that of thrombelastography, and according to some authors it may be of considerable value in the detection of thrombophilic states.[36, 37] When thrombelastography was employed in this study, however, there was no evidence of a trend toward hypercoagulability of the blood in any of the groups of subjects, either before or after the ingestion of fat. In this regard, Nitzberg et al.[33] were previously unable to demonstrate consistent acceleration of the whole blood clotting time in normal subjects during alimentary lipemia, when this method was used. Recently Sheehy and Eichelberger,[38] employing this technic in 30 healthy soldiers, were likewise unable to find consistent evidence of hypercoagulability following the ingestion of fat.

The Stypven time was the only coagulation test in this series that was constantly altered in the presence of hyperlipemia. Thus there was acceleration of the Stypven time to a greater or lesser extent in all groups of subjects following the fatty meal. This is in agreement with the results of several workers including Fullerton et al.,[8] O'Brien,[39] Merskey and Nossell,[20] and Mustard.[11] Furthermore, there was marked acceleration of the Stypven time in the fasting state in all the patients with idiopathic hyperlipemia when compared with the fasting values in the normal subjects and in the patients with primary hypercholesteremia a finding similar to that encountered by Sohar et al.[15] It might therefore be suggested that the unique behavior of this coagulation test in the fasting state in the group of patients with idiopathic hyperlipemia was related to the high serum triglyceride levels found in this group, inasmuch as these lipid values were normal in the fasting state in the other 2 groups of individuals. Moreover, the acceleration of the Stypven time after the fatty meal was always accompanied by a rise in the serum triglycerides. Indeed, Sohar et al.[15] concluded that there is in fact a close correlation between the Stypven time and the concentration of triglycerides in the serum. These observations could not be *fully* substantiated in our series, however, since analysis of the results of individual subjects clearly demonstrated that there was *no strict quantitative relationship* between the Stypven time and the serum triglycerides in the majority of individuals either in the fasting state or postprandially. Similarly, there was some association, though not a strict correlation, between the Stypven time and the serum turbidity. This is not surprising when it is realized that the turbidity of the serum is a reflection of the concentration of chylomicra, which in turn are mainly composed of triglycerides and to a lesser extent of phospholipids and lipoproteins. When the serum fatty acids are considered, it is obvious that, as with the serum triglycerides, there was some association between accelerated Stypven times and the concentration of these lipids in the serum, although again there was no strict quantitative relationship. There was clearly no association between the Stypven time and the serum cholesterol or phospholipid levels in any of the groups of patients either in the fasting state or following the fatty meal. The absence of an association between the Stypven time and the fasting serum cholesterol levels is further suggested by the demonstration of essentially similar Stypven times in a group of 20 hospital patients with either high or normal cholesterol values.[40] However, the lack of association in this series between the Stypven time and the serum phospholipids

es not necessarily exclude the possible effect ingested phospholipids on blood coagulaon. O'Brien[41] was able to demonstrate apreciable acceleration of the postprandial ypven time after feeding small quantities phospholipids to normal subjects even ough the actual levels of serum phosphopids remained essentially unchanged.

It is difficult to determine the significance the acceleration of the Stypven time by yperlipemia, since the test itself is highly rtificial and hence unphysiologic. Thus, ussell viper venom is a thromboplastic agent hich rapidly converts prothrombin to thromin in the presence of optimal concentrations labile and Stuart factor . In addition platelets, platelet lipid fractions, phospholipids, nd perhaps fatty acids accelerate this reaction. For example, Poole[42] using platelet-poor plasma was able to demonstrate acceleration of the Stypven time by various fatty acids. O'Brien[43] confirmed this observation, but found that the phospholipids were even more potent in this respect. Subsequently, Poole and Robinson[44] showed that chylomicra led to shortening of the Stypven time, and they attributed this effect to the presence of small quantities of ethanolamine phosphatide contained within them. Recently, Kingsbury and Morgan[45] found that the recalcification time of plasma was influenced by the chylomicra and they were further able to show that the factor responsible for the actual shortening of the calcium clotting time consisted of the phospholipid fraction derived from the chylomicra. All this evidence certainly suggests that phospholipids, or one of the components thereof, such as ethanolamine phosphatide, may play an important role in the acceleration of blood clotting. Further evidence is provided by O'Brien,[41] who reorted that ingested phospholipids were about times as active as triglycerides in causing celeration of the Stypven time. He[41] sugsted that phospholipids inactive with reect to the Stypven time when added in the st tube, become hydrolyzed and activated ter ingestion. Indeed O'Brien[39] claimed at there is in fact a strict quantitative relationship between the concentration of "active phospholipids" in the blood and the Stypven time. He concluded[46] that a postprandial increase in the serum of ethanolamine phosphatide, or similar substances such as phosphatidyl-serine or inositol phosphatide, is probably responsible for the maximal shortening of the Stypven clotting time. Since these alterations in the serum phospholipids are not apparent when, as in this series of patients, the usual chemical methods are used, it would seem essential that more sensitive procedures be introduced for the detection of such changes. It is possible that paper chromatography will be useful in isolating and identifying the various phospholipid fractions after a fatty meal. In this regard Troup and Reed[47] using such a method were unable to demonstrate the presence of these substances in the plasmas of normal individuals. In any event, the fact that it was not possible to demonstrate a strict quantitative relationship between the Stypven time and the serum triglycerides in this series could well be due to the presence in hyperlipemic blood of other factors, such as for example, a cephalin fraction, which may play an important role in the development of hypercoagulability of the blood.

Since the role of platelets in blood coagulation is well established, it was decided to employ platelet-free systems in this study. It was considered that the presence of thromboplastic factors, introduced into the plasma as the result of a fatty meal, could be evaluated more clearly if platelet fractions of a similar thromboplastic nature were excluded. However, platelet-poor systems in vitro are unphysiologic, inasmuch as platelets or their fractions undoubtedly play an essential part in the development of intravascular thrombosis. The fact that platelet fractions, namely cephalin and lecithin, even in very small quantities possess a marked activating effect upon blood coagulation was shown by Chargaff et al.[48] in 1936. More recently, O'Brien[49] has reported that one of the active clotting factors in platelets is similar to ethanolamine phosphatide while Wallach et al.[50] have ac-

tually demonstrated the presence of this substance in the platelets by means of paper chromatography. On the other hand, Troup and Reed[47] have found that weight for weight serine phosphatide is much more active than ethanolamine phosphatide as a platelet thromboplastic factor. Be that as it may, it is obvious that platelets do contain potent thromboplastic materials which must be considered.

Although the fibrinolytic activity of the blood, as measured by the Fearnley[25] technic, was not decreased in this series in the presence of hyperlipemia either in the fasting or postprandial states, it is of considerable interest that hyperlipemia appeared to be associated with some reduction of the profibrinolytic activity of the plasma. This was observed primarily in patients with constant hyperlipemia, although there was suggestive evidence of this occurring even in normal subjects after ingestion of the fatty meal. It might therefore be assumed that this diminished profibrinolysin level was in some way related to the high levels of triglycerides (or the other constituents of chylomicra), which are responsible for the increased serum turbidity found in such states of hyperlipemia. In fact there appeared to be some association, although not a strict correlation, between the length of the streptokinase fibrinolysis time and the serum triglyceride levels as well as with the serum turbidity. In spite of this trend, however, the prolongation of the fibrinolysis time in this series was not considered to be of significance in the majority of these individuals. These results, which suggest some association between hyperlipemia and reduced fibrinolysis, were based upon a method that measured the fibrinolytic activity of the plasma only indirectly (i.e., fibrinolysis was activated by streptokinase). Moreover, the mere inhibition of fibrinolysis by fat in such an artificial system does not explain the exact mechanism of the interaction between the fat and the various fibrinolytic precursors.

Only a few reports have appeared with reference to the effect of ingested fat on blood fibrinolysis. The prevailing opinion is that fats do inhibit fibrinolysis, although there is no agreement as to which of the serum lipids is directly responsible for this phenomenon. Thus Greig and Runde[13] have emphasized the role of the beta lipoproteins and the chylomicra in the inhibition of fibrinolysis, while in an earlier communication Greig[12] was able to find a direct association between fibrinolysis and the serum turbidity. Admittedly, it was not possible in the present study to demonstrate such conclusive evidence of inhibition of fibrinolysis by fats as was obtained by Greig,[12] but this failure may be due in part to the different methods employed in assessing fibrinolytic activity. In this respect, Greig[12] measured fibrinolysis by a modification of the method of Biggs and MacFarlane[51] and Bidwell.[52] Recently, however, Scott and Thomas[53] reported significant prolongation of the streptokinase fibrinolysis time in rabbits following the ingestion of butter fat. Yet another approach has been introduced by Kwaan and MacFadzean,[54] who found that feeding cholesterol to rabbits inhibited fibrinolysis in vivo. It is not clear from their communication what effect the ingested cholesterol had on the various serum lipids, but certainly in our own study the patients with primary hypercholesteremia did not show any inhibition of fibrinolysis in the fasting state.

At the time of these studies 3 patients with idiopathic hyperlipemia (cases 1, 3, and 5) and 3 patients with primary hypercholesteremia (cases 10, 17, and 18) had clinical and electrocardiographic evidence of ischemic heart disease, amounting in 3 patients (cases 1, 10, and 17) to acute coronary artery disease. In none of these patients was there evidence to suggest that the behavior of the blood clotting or fibrinolytic systems differed from that of the other patients within the same group, either in the fasting state or in response to a fat-loading meal. It is possible of course that the close association between primary hypercholesteremia and coronary artery disease does not depend upon the presence of hypercoagulability of the blood or diminished blood fibrinolysis. Indeed it still remains likely that the increased incidence

f coronary artery disease in these patients s primarily due to the formation of plaques n the intima, which in turn lead to an increased risk of secondary occlusive thrombi n the coronary arteries. Another point is hat patients with primary hypercholesterenia may be more liable to coronary atherosclerosis than those with idiopathic hyperlipemia who do not have elevated levels of cholesterol n the serum. (The 3 hyperlipemic patients with concomitant ischemic heart disease in his series had high serum cholesterol levels.) If this is so, the effect of hyperlipemia on coagulation and fibrinolysis, as observed in this series, may not be of major importance in the development of ischemic heart disease.

Recently, other mechanisms that may help to account for the role of the blood lipids in the development of arterial disease have been suggested by the introduction of new and ingenious technics. Thus Goldberg and Morantz[55] were able to demonstrate actual infiltration of the connective-tissue cells of the elastic lamina in the aortas of young chicks with lipid particles from a perfusing stream of lipid-enriched blood, while Rutstein et al.[56] showed that lipids (cholesterol) were engulfed by the cells of human aortic intima grown in artificial culture media. For the present, however, the exact mode of development of atherosclerosis either in patients with abnormal lipid metabolism or in other individuals must remain conjectural. Moreover, in assessing the results in this study, it must be remembered that conditions in the test tube do not necessarily reflect those present in vivo. For example, the majority of coagulation tests in current use are primarily measuring factors that govern the speed of coagulation rather than control its initiation. Be that as it may, it is clear that in this series hyperlipemia (i.e., lactescent serum with elevated levels of serum triglycerides) was usually associated with accelerated Stypven times and frequently also with prolonged profibrinolysin times. These results suggest that there may be some relationship between hyperlipemia, increased coagulability of the blood and reduced blood fibrinolytic activity. However, the real significance of these in vitro findings with regard to clinical coronary artery disease remains obscure.

Summary

The clotting and fibrinolytic activity of the blood were studied before and after a meal containing 85 Gm. of fat. There were 3 groups of subjects; 9 patients with idiopathic hyperlipemia, 10 patients with primary hypercholesteremia, and 10 normal subjects. Simultaneous lipid studies were performed in an attempt to correlate the coagulation and fibrinolysis values with changes in the various serum lipid levels.

The results of the coagulation studies were divided into 2 categories. The first was composed of the data obtained by measuring specific coagulation factors. The values obtained for these factors were within normal limits before and after the fatty meal in the 3 groups of subjects.

The second category comprised the results of those procedures that measure the over-all coagulability of the blood (or plasma) with or without the addition of thromboplastic material. The results of all these determinations, with the exception of the thromboplastin generation test and the Stypven time, were within normal limits in the fasting state and remained essentially unchanged after the fatty meal in the 3 groups of subjects.

The thromboplastin generation test gave essentially inconclusive results although there appeared to be a tendency for the hyperlipemic and hypercholesteremic groups to develop a more potent thromboplastin in the fasting state.

The Stypven time (Russell viper venom test) was the *one* coagulation test that almost always showed significant changes in the presence of hyperlipemia. Thus it was markedly accelerated (i.e., shortened) in the fasting state in all the patients with idiopathic hyperlipemia. In addition, the Stypven time was accelerated to a greater or lesser extent in all groups of subjects following the fatty meal. Comparison of these results with the serum lipid levels showed that there was *some*

degree of correlation, although not a strict quantitative relationship, between the Stypven time values and the serum triglyceride levels (and the fatty acid levels to a lesser extent) as well as with the turbidity of the serum in all groups of subjects before and after the fatty meal. No correlation was found between the Stypven time and the serum cholesterol or phospholipid levels.

Two methods were employed to assess the fibrinolytic activity of the blood. Method 1, which measured blood fibrinolysis directly, gave variable and inconclusive results. Method 2, which determined the fibrinolytic activity of plasma after activation with streptokinase (in vitro), showed that prolonged streptokinase fibrinolysis times occurred under circumstances similar to those associated with accelerated Stypven times. Thus there appeared to be an association of the fibrinolysis time with the serum triglyceride levels as well as with the serum turbidity.

The behavior of the blood clotting and fibrinolytic systems in the 6 patients in this series who had evidence of coronary artery disease did not differ from that of the other individuals within the same groups either in the fasting state or after the fatty meal.

Summary

Hyperlipemia in general leads to acceleration of blood clotting, as measured by the Stypven time, as well as to inhibition of blood fibrinolysis.

The inability to demonstrate a strict quantitative relationship between the Stypven time and the serum triglycerides in this series suggests that other factors, such as a cephalin fraction, may also play an important role in the development of hypercoagulability of the blood. The same may hold true for the association between hyperlipemia and reduced fibrinolytic activity.

The development of coronary atherosclerosis in patients with primary hypercholesteremia may depend on factors other than those of increased blood clotting or decreased blood fibrinolytic activity.

The conclusions with regard to the effect of serum lipids on coagulation and fibrinolysis in this series have been based essentially on highly artificial tests. The final elucidation of the exact relationship between the serum lipids and the coagulability of the blood, and its possible connection with coronary artery disease, must await further studies.

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Summario in Interlingua

Hyperlipemia, a generalmente parlar, resulta in acceleration del processo coagulatori del sanguine secundo le mesuration del tempore a stypven e etiam in inhibition del fibrinolyse de sanguine.

Le impossibilitate de demonstrar in le presente serie de casos un relation strictemente quantitative inter le tempore a stypven e le triglyceridos del sero suggere que altere factores, como per exemplo un fraction de cephalina, ha etiam un rolo importante in le disveloppamento de hypercoagulabilitate de sanguine. Le mesmo es possibilemente ver pro le association inter hyperlipemia e un reducite activitate fibrinolytic.

Le disveloppamento de atherosclerosis in patientes con hypercholesterolemia primari depende de factores altere que le augmentate coagulation de sanguine o le reducite activitate fibrinolytic del sanguine.

Le conclusiones con respecto al effecto de lipidos seral super le coagulation e le fibrinolyse in le presente serie es basate essentialmente super tests de character multo artificial. Le ultime elucidation del relation exacte inter le lipidos del sero e le coagulabilitate del sanguine e su connexion possibile con morbo de arteria coronari debe attender studios additional.

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Effects of Intravenous Hydration and Pitressin on Renal Function in Subjects with Essential Hypertension

By WILLIAM HOLLANDER, M.D.

Various abnormalities in metabolism of water and electrolytes have been noted in patients with arterial hypertension and have variously been considered as causes or results of the hypertension. In this paper new data on these relationships are presented by a study of the changes in renal function produced by intravenous hydration, Pitressin, and lowering of the blood pressure.

A NUMBER of workers have shown that the capacity to excrete sodium, as indicated by the rate of excretion of an intravenous salt load, is appreciably greater in hypertensive than in normotensive individuals.[1-3] In addition, it has been demonstrated that effective antihypertensive treatment is capable of reducing the sodium excretory capacity of hypertensive subjects towards normal.[4, 5] These findings support the concept that the arterial pressure per se may play an important role in the control of sodium excretion. They also suggest that certain other disturbances in electrolyte and water metabolism in arterial hypertension[6] may be the result and not necessarily the cause of an elevated blood pressure.

In the present study of water excretion in essential hypertension a disturbance is described that appears in part to be related to the elevation of arterial pressure.

MATERIAL AND METHODS

The renal responses to intravenous hydration and Pitressin were tested in 11 hypertensive and 9 control subjects. In addition, 9 of the hypertensive subjects were restudied after treatment with antihypertensive drugs.

The 9 control subjects had no history of renal disease or of hypertension and were considered normal. Their surface areas and weights were comparable to those in the hypertensive group.

The 11 subjects with essential hypertension had a sustained elevation of the blood pressure with grade 1 to 3 retinopathy but without complicating congestive heart failure. However, 4 subjects had electrocardiographic and roentgenologic evidence of left ventricular enlargement as well as 1+ to 2+ albuminuria. In addition 3 of these subjects had an elevation of the blood urea nitrogen ranging from 35 to 84 mg. per cent. The dietary intake of salt was not restricted in either the hypertensive or normotensive subjects.

After an 8 to 12-week control period during which the hypertensive subjects received only placebos, treatment was started with antihypertensive drugs and continued for 8 to 16 weeks. The type and dosage of drugs together with their effects on blood pressure are summarized in table 1. The blood pressures were measured weekly in the sitting position.

TABLE 1.—*Summary of Drug Treatment of the Hypertensive Group*

	Control period		Therapy			
Subject	Average blood pressure (mm. Hg)	Duration (weeks)	Average blood pressure (mm. Hg)	Duration (weeks)	Drugs	Dosage (mg./day)
R.M.	172/114	10	152/88	8	Hydralazine	400
I.C.	200/112	12	179/102	12	Hydralazine	400
B.C.	169/108	12	150/88	8	Hydralazine	400
E.C.	184/118	12	138/74	12	Reserpine	0.5
A.G.	209/115	12	182/100	12	Reserpine	0.5
H.B.	180/115	12	142/81	16	Reserpine	0.5
B.W.	247/148	8	164/96	8	Pentolinium	180
R.A.	238/137	8	180/118	12	Pentolinium	420
A.W.	260/152	8	172/111	12	Pentolinium	420
Mean	206/124	10	162/95	11		
S.D.	±34/17	±1.9	±17/14	±2.7		

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TABLE 2.—*Mean Data and Statistical Analysis*

	Control	Maximal diuresis	Pitressin antidiuresis	Recovery
V (ml./min.)				
Normal group	0.96±0.2*	16.2±1.1	6.8±1.4	16.0±1.8
Hypertensive group+	1.2±0.2	11.4±0.7	5.2±0.6	12.6±0.6
Mean difference	+0.24±0.2	−4.7±1.2	−1.6±1.6	−3.4±1.9
p	0.3	<0.01	0.3	0.1
Hypertensive group (before treatment)	1.2±0.1	10.7±0.9	5.1±0.5	11.8±1.0
Hypertensive group (during treatment)	1.3±0.2	13.6±1.1	6.4±0.7	13.7±1.1
Mean difference	+0.08±0.2	+2.9±0.8	+1.3±0.8	+1.9±0.7
p	0.7	<0.01	0.2	0.03
$U_{NA}V$ (μEq./min.)				
Normal group	133±26	230±22	235±30	280±57
Hypertensive group+	205±47	223±71	209±50	242±38
Mean difference	+71±54	−8±74	−26±58	−38±69
p	0.2	>0.9	0.7	0.6
Hypertensive group (before treatment)	187±43	245±64	232±48	250±34
Hypertensive group (during treatment)	243±62	324±51	326±72	297±61
Mean difference	+56±66	+79±74	+94±83	+47±62
p	0.4	0.3	0.3	0.5
U_KV (μEq./min.)				
Normal group	65±15	56±16	55±17	53±12
Hypertensive group+	58±8	41±6	44±4	39±4
Mean difference	−7±17	−16±17	−11±17	−14±13
p	0.7	0.4	0.6	0.4
Hypertensive group (before treatment)	61±8	50±10	52±9	46±8
Hypertensive group (during treatment)	72±15	52±9	52±7	40±4
Mean difference	+11±9	+2±10	+0.1±7	−6±8
p	0.3	0.8	0.9	0.4
PAH clearance (ml./min./1.73 M.^{2})				
Normal group	567±21	606±22	563±26	627±30
Hypertensive group+	425±21	433±23	434±28	457±25
Mean difference	−142±30	−173±32	−129±38	−170±39
p	<0.01	<0.01	<0.01	<0.01
Hypertensive group (before treatment)	383±46	390±47	392±49	412±50
Hypertensive group (during treatment)	398±44	437±51	437±50	472±66
Mean difference	+14±8	+47±20	+45±18	+60±28
p	0.1	0.05	0.05	0.08

(*Continued on next page*)

TABLE 2.—(*Continued*)

	Control	Maximal diuresis	Pitressin antidiuresis	Recovery
Inulin clearance (ml./min./1.73 M.²)				
Normal group	111±3	118±4	104±5	119±5
Hypertensive group†	93±5	90±6	91±6	94±6
Mean difference	−18±6	−28±7	−14±8	−25±8
p	0.01	<0.01	0.1	0.01
Hypertensive group (before treatment)	87±7	84±7	85±7	88±8
Hypertensive group (during treatment)	85±7	84±6	84±6	89±7
Mean difference	−3±3	−0.1±4	−0.6±3	+0.8±2
p	0.3	>0.9	0.8	0.8

*Figures in italics are standard error.

†Group does not include the 3 subjects with severe renal disease.

The subjects were studied in the morning in the postabsorptive state while lying supine. Throughout the study nothing was permitted by mouth. Urine was collected through an indwelling catheter. At the end of each collection the bladder was washed out with 20 ml. of distilled water and was then completely evacuated with air. After standard priming doses, a sustaining infusion containing inulin (3.3 per cent) and paraaminohippurate (1 per cent) in 3.5 per cent glucose in water was started and given at the rate of 1.2 ml. per minute. Every 30 minutes blood samples were obtained for the determination of inulin, paraaminohippuric acid, sodium, potassium, and hematocrit. Following the control observations, which extended over 3 urine collection periods of 10 to 15 minutes each, an infusion of 5 per cent glucose in water was started and continued throughout the experiment at the approximate rate of 14 ml. per minute. During this infusion urine collections were continued at intervals of 10 to 15 minutes. When urine flow reached a steady maximal rate, Pitressin (Parke, Davis and Company, Lot no. 161) was injected rapidly into the infusion tubing in a dose of 1 milliunit per Kg. of weight. After the ensuing "Pitressin antidiuresis" the experiment was continued until a maximal rate of excretion of urine was resumed.

The chemical methods have been previously described.[4]

RESULTS

The renal responses to intravenous 5 per cent glucose in water in the normotensive and hypertensive groups are summarized in tables 2 and 3.

Urine Flow (V)

The control urine flows were comparable in the normotensive and hypertensive groups. However, the maximal diuresis produced by the infusion of 5 per cent glucose and water was appreciably lower in the hypertensive than in the normotensive group. These differences were significant even though the 3 hypertensive subjects who had advanced renal disease were not included in the statistical analysis of the groups. The time at which urine flow reached its peak level was not significantly different in the control and hypertensive groups. Likewise the percentage reduction in urine flow and the duration of the antidiuresis produced by Pitressin did not differ significantly in the groups. In the recovery period the average urine flow was lower, but not significantly, in the hypertensive than in the normotensive group.

When compared with normotensive and hypertensive subjects without advanced renal disease, hypertensive subjects with severe renal disease had a considerable reduction in the maximal water diuresis and appeared to be unresponsive to Pitressin.

Following antihypertensive drug treatment, the average maximal rate of urine excretion in the hypertensive group significantly increased to 13.6 ml. per minute as compared

TABLE 3.—*Water Excretory Responses to Intravenous Hydration and Pitressin*

	Time to maximal diuresis (min.)	Maximal diuresis (ml./min.)	Pitressin antidiuresis (ml./min.)	% reduction in urine flow by Pitressin	Duration of Pitressin antidiuresis (min.)
Normal group	80±17*	16.2±3.3	6.8±3.5	47±17	45±16
Hypertensive group	79±11	11.4±1.9	5.2±1.7	58±51	54±13
p	0.8	<0.01	0.3	0.3	0.3
Hypertensive group (before treatment)	81±13	10.7±2.8	5.1±1.6	49±20	53±13
Hypertensive group (during treatment)	77±21	13.6±3.3	6.4±2.2	52±15	52±11
p	0.4	<0.01	0.2	0.6	0.9

*± standard deviation.

with 10.7 ml. per minute before treatment. In the recovery period, likewise, the urine flow was significantly higher after than before treatment. The other water excretory responses were not significantly changed by treatment.

Sodium Excretion ($U_{Na}V$)

The excretion of sodium at rest, during the infusion of 5 per cent glucose in water and after the administration of Pitressin was not significantly different in the normotensive and hypertensive groups. During the infusion the mean sodium excretion increased in both groups and was not significantly reduced by Pitressin ($p > 0.5$). Although the mean increase in sodium excretion was higher in the normotensive than in the hypertensive group without severe renal disease, it was not significantly different in the groups ($p = 0.19$).

During antihypertensive treatment, the excretion of sodium at rest and in the experimental periods was not significantly different from the sodium excretion recorded before treatment.

Potassium Excretion (U_KV)

The excretion of potassium in the control and experimental periods was not significantly different in the normotensive and hypertensive groups. The mean potassium excretion decreased in both groups during the water diuresis, but did not change appreciably after as compared with before the administration of Pitressin.

After antihypertensive therapy potassium excretion during intravenous hydration and following the administration of Pitressin was not significantly different from the values obtained before treatment.

PAH and Inulin Clearances

The PAH clearance (renal plasma flow) and inulin clearance (glomerular filtration rate) were significantly lower in the hypertensive than in the normotensive group during the control period as well as during maximal diuresis. In both groups the renal plasma flow did not change significantly during the experiment ($p > 0.14$). However, the glomerular filtration rate did increase significantly in the normotensive ($p = 0.05$) but not in the hypertensive group ($p = 0.09$) at the peak of the water diuresis. In response to Pitressin neither group had a significant alteration in glomerular filtration rate ($p > 0.07$).

The control renal plasma flow and glomerular filtration rate were not significantly altered by antihypertensive treatment. The glomerular filtration rate in the experimental periods also was not significantly different after than before treatment. However, the renal plasma flow was significantly higher during the periods of maximal diuresis and antidiuresis after than before treatment.

Blood Pressure

The average blood pressure in the hypertensive group was 206/124 mm. Hg as compared to 124/79 mm. Hg.

Following drug treatment of the hypertensive group, the average blood pressure was significantly reduced by 44/29 mm. Hg.

Discussion

The observation that the maximal rate of urine flow produced by intravenous hydration was significantly less in hypertensive than in normotensive individuals suggests a reduction in water excretory capacity in arterial hypertension. The disturbance in water excretion was associated with a significant reduction in glomerular filtration rate and was most marked in those hypertensive subjects who had the severest impairment in this function. It therefore appears likely that a reduction in glomerular filtration rate is one of the factors responsible for the reduced water diuresis. Solute excretion also has been reported to be capable of altering the height of a water diuresis.[7, 8] Although it was not measured, sodium and potassium excretion, which contributes to solute excretion, appeared to be comparable in the normotensive and the treated and untreated hypertensive subjects. In addition to a reduction in renal hemodynamic function, an elevated blood pressure appears to be another important factor that might operate to reduce maximal urine flow, since a significant increase in water diuresis occurred without a change in glomerular filtration rate following a reduction in blood pressure with antihypertensive drugs. It is unlikely that the increases in urine flow following treatment were due to a direct drug effect on renal function, since the same effects were produced by several different drug regimens.

The manner in which a change in blood pressure might effect water excretory capacity is not clear. It is conceivable, however, that arterial pressure may influence the function of a number of organs that regulate urine excretion such as the kidney, and the adrenal and pituitary glands. An alteration in posterior pituitary function or in Pitressin metabolism as a cause of impaired water excretion was not completely excluded in the present study. Nevertheless, the finding that hypertensive subjects did not differ from control subjects in the time of onset of the maximal rate of urine excretion or in the intensity and duration of the Pitressin antidiuresis suggests that Pitressin is normally inactivated in uncomplicated arterial hypertension.

Ek[9] has likewise found that a constant infusion of 5 per cent glucose in water produces a diuresis that is significantly lower in hypertensive than in normotensive individuals. In addtion he observed that hypertensive subjects in contrast to normotensive controls had striking increases in renal plasma flow, glomerular filtration, and sodium excretion during water diuresis. In the present study increases in sodium excretion and renal hemodynamic function during intravenous hydration were slight and not significantly greater in the hypertensive than in the normotensive group. These differences may be related to the rate of administration of the intravenous water load, that in the present study being considerably less than that in the previously reported study.

Summary

Urine flow, electrolyte excretion, and renal hemodynamic function were compared in normal and hypertensive individuals before and during a constant infusion of 5 per cent glucose in water and in response to intravenous Pitressin. The maximal urine flow produced by intravenous hydration was significantly less in the hypertensive than in the normotensive group. However, the renal responses to intravenous Pitressin were comparable in the 2 groups. The reduced water diuresis in arterial hypertension was associated with a significant reduction in renal plasma flow and glomerular filtration rate but not in salt excretion. The maximal rate of urine excretion significantly increased toward normal following antihypertensive drug treatment. It appeared to result from an alteration in renal tubular activity, since the glomerular filtration rate was not significantly different before and after treatment. The findings suggest that an elevated arterial pressure in addition to a reduction in renal hemodynamic function

may operate to reduce water excretory capacity in essential hypertension.

SUMMARIO IN INTERLINGUA

Le fluxo de urina, le excretion de electrolytos, e le function hemodynamic del renes esseva comparate inter subjectos normal e hypertensive ante e durante un infusion constante de 5 pro cento de glucosa in aqua e in responsa al administration intravenose de Pitressina. Le fluxo maximal de urina producite per hydratation intravenouse esseva significativemente plus basse in le gruppo hypertensive que in le gruppo normotensive. Tamen, le responsas renal a Pitressina intravenose esseva comparabile in le 2 gruppos. Le reducite diurese de aqua in hypertension arterial esseva associate con un reduction significative del fluxo de plasma e del filtration glomerular in le renes sed non del excretion de sal. Le intensitate maximal del excretion de urina montava significativemente in le direction de valores normal post tractamento con drogas antihypertensive. Isto pareva esser le resultato de un alterate activitate del tubulos renal, proque le intensitate del filtration glomerular non differeva significativemente ante e post le tractamento. Le constatationes pare indicar que un elevate pression arterial, a parte un reduction del function hemodynamic del renes, participa in le reduction del capacitate pro le excretion de aqua in hypertension essential.

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The present remarkable position in applied science and in industrial trades of all sorts has been made possible by men who did pioneer work in chemistry, in physics, in biology, and in physiology, without a thought in their researches of any practical application. The members of this higher group of productive students are rarely understood by the common spirits, who appreciate as little their unselfish devotion as their unworldly neglect of the practical side of the problems.—WILLIAM OSLER, M.D. *The Student Life. Farewell Address to American and Canadian Medical Students.* Med. News. (N. Y.), 1905.

Action of Nitroglycerin on the Coronary Circulation in Normal and in Mild Cardiac Subjects

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With the technical assistance of Morris H. Smith and Elin Alexanderson

Nitroglycerin has been used extensively as a coronary vasodilator. Its remarkable clinical effect has been presumed to be related to a direct action on the smooth muscle of the coronary arteriole. No observations have been made of nitroglycerin action on the coronary circulation in man. This report presents studies of changes induced by the drug in 10 normal or nearly normal subjects. The authors present evidence that although coronary vasodilatation does indeed occur, it appears to be secondary to changes in myocardial oxygen requirements. Hemodynamic observations revealed a general decrease in pressures in both peripheral and pulmonary circuits; caution is urged concerning the occasional severe hypotensive effects of nitroglycerin.

IN 1867 Sir Lauder Brunton first reported the use of nitrites in the relief of hypertensive crisis and status anginosus.[1] At that time, he attributed the remarkable clinical effect of the drug to its actions of peripheral vasodilatation and in lowering blood pressure. It remained for other investigators[2, 3] to demonstrate in the experimental animal that this dilatation was not confined to the periphery, but in fact took place in the coronary vessels as well. In 1940 Essex and co-workers,[4] and Boyer and Green[5] independently reported that nitroglycerin increased coronary blood flow in experimental animals. In 1947, however, Eckenhoff and co-workers[6] found only inconstant changes in coronary blood flow when more elaborate technics were used. They also stated that the coronary vasodilator effect in the dog persisted only so long as the blood pressure did not fall. Eckstein and his co-workers[7] and Sarnoff, Case, and Macruz[8] have measured myocardial oxygen consumption before and after nitroglycerin in the dog and found no changes. Despite its widespread clinical use and the many assumptions regarding its mode of action, there have been no published reports concerning the effect of nitroglycerin on the coronary circulation in man. It is the purpose of this communication to describe such changes and also to report on the general circulatory effects of sublingually administered nitroglycerin.

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MATERIALS AND METHODS

Ten patients were studied by cardiac catheterization. One patient had clubbing with normal pulmonary and cardiac diagnostic studies; 1 had a small atrial septal defect; 1 a grade-I diastolic murmur of aortic insufficiency without changes in blood pressure; 2 had basal systolic murmurs of grade-II intensity without other abnormality; 1 had a functional apical grade-II systolic murmur, and 4 had completely normal cardiac examinations. These patients had had hepatic vein catheterization with measurement of blood flow and pressure for evaluation of recovery from an earlier acute hepatitis; all studies of liver function were normal.

Cardiac catheterization was performed in the usual fashion: an indwelling no. 17 Riley needle was inserted into the brachial artery. Any diagnostic studies that were required were carried out before this investigation.[9] Pressures were measured in the pulmonary wedge position, pulmonary artery, right ventricle, and right atrium before and after administration of nitroglycerin, by means of a Statham P-23D manometer, recorded directly on a Sanborn twin-channel recorder. Cardiac outputs were measured by the direct Fick method in all, and by indicator-dilution technics in 5.[10] The catheter was then inserted into the

coronary sinus. Coronary blood flow calculated as ml./100 Gm. left ventricular muscle/min. was measured by the nitrous oxide technic[11] as modified by Goodale and Hackel.[12] Four minutes after 0.6 mg. of nitroglycerin had been given sublingually, the second flow was begun with samples collected continuously from 0 to 1 min., 1:15-1:45, 2.45-3:15, 4.45-5:15, 6:45-7:15, following cessation of nitrous oxide breathing. From this, a nitrous oxide curve could be constructed[12] of the veno-arterial nitrous oxide difference during "desaturation" of nitrous oxide from the myocardium.* During the 7-minute period required for determining coronary flow, arterial pressure, heart rate, and indicator-dilution output were measured. Following determination of the coronary flow after nitroglycerin, the catheter was returned to the pulmonary artery in 8 patients.

Blood samples drawn from the coronary sinus, pulmonary artery, and brachial artery were analyzed for oxygen and carbon dioxide content by the technic of van Slyke and Neil,[14] and pH was measured in a Cambridge pH meter. Partial pressures of oxygen and carbon dioxide were calculated via conversion factors devised by Milch et al.[15] Mean systolic and mean diastolic pressures and systolic and diastolic time periods were measured on the brachial arterial pressure pulse recorded during the coronary flow.

By means of formulas described elsewhere[16] left and right ventricular work were calculated as Kg.M./min./M.^{2} and systemic and pulmonary resistances were calculated as dynes sec. cm.$^{-5}$ Coronary vascular resistance was calculated by the standard formula[11]:

$$CVR_m = \frac{(BAm - RAm)}{CF} \times 1332$$

where

CVR_m = mean coronary vascular resistance (dyne sec. cm.$^{-5}$)
BAm = brachial arterial mean pressure, mm. Hg
RAm = right atrial mean pressure, mm. Hg
CF = coronary flow, ml./100 Gm./sec.
1332 = conversion of mm. Hg to dynes/cm.^{2}

Coronary vascular resistance was also computed according to the following formula[9] in order to introduce the factor of shortened diastolic time:

$$CVR_d = \frac{(BAdm - RAm)}{CF \times 0.75} \times DFP \times 1332$$

where

CVR_d = diastolic coronary vascular resistance (dynes sec. cm.$^{-5}$)
$BAdm$ = brachial arterial diastolic mean pressure (mm. Hg)
DFP = diastolic filling period, sec./min.
0.75 = fraction of coronary flow occurring in diastole[17]

Resistances calculated at widely divergent perfusion pressures may not necessarily be comparable.[18] Perfusion pressure, however, decreased only 10 per cent in this group. Furthermore, changes in resistance in this group will be ultimately compared to changes in resistance in other groups of patients with similar declines in blood pressure following nitroglycerin.

Myocardial oxygen consumption was computed as the product of oxygen extraction and coronary flow. This was calculated per 100 Gm. muscle and for the total left ventricular weight by the formulas of Smith*[19] with an error estimated at ± 10 per cent. Myocardial oxygen consumption was also computed per second of systolic contraction;[9] oxygen consumption per systolic second was then divided by Kg.M. of work per minute. These arithmetical indices served to relate oxygen consumption to the hemodynamic parameters at the moment.†

Mechanical efficiency was calculated both per 100 Gm. muscle and for the total left ventricle according to previously described formulas.[17]

Observations

General Hemodynamic Changes (Table 1). Cardiac output averaged 3.3 L./min./M.^{2} and

*Previous studies have shown that nitroglycerin begins to act between 1 and 5 minutes after sublingual administration,[13] as evidenced by fall in blood pressure, change in pulse pressure contour, and increase in cardiac rate. Its peak effect is between 5 and 10 minutes and lasts from 15 to 30 minutes. Continuous direct monitoring of blood pressure and heart rate served to indicate onset and persistence of circulatory effects of nitroglycerin during the flow study which was carried out between the fourth and the eleventh minute. Unpublished studies measuring coronary blood flow within 1 minute of sublingual administration of the drug showed no deviation from the procedure reported herein.

*0.23 per cent of body weight in kilograms for males, 0.21 per cent for females.

†The numbers so derived obviously have no biological significance, but do indicate the manner in which oxygen is expended. Time spent in contraction and the amount of work done per minute are independent variables each affecting total oxygen utilization.[9] For example, patients with different cardiac rates having identical work outputs per minute will have different myocardial oxygen consumptions per minute.[9] Therefore, when variations in oxygen consumption have been arithmetically related to variations in heart rate and work, any deviations from the normal values suggest a non-hemodynamic factor influencing myocardial oxygen metabolism. For this artificial derivation "basal non-contractile" cardiac oxygen consumption is assumed to be constant and has not been subtracted from the total figure.[20]

TABLE 1.—*Action of Nitroglycerin on Systemic and Pulmonary Hemodynamics*

Patient no.	Age	Diagnosis	Body surface area (M^2)	Heart rate per min.	Cardiac output (L./min./M^2)	Pressures (mm. Hg)						Ventricular work (Kg.M./min./M^2)		Vascular resistance (dyne sec. $cm.^{-5}$)	
						Brachial artery									
						Systolic mean	Mean	Diastolic mean	Pulmonary artery mean	Right atrial mean	Pulmonary capillary mean	Left	Right	Pulmonary	Systemic
1	34	Clubbing ? cause		70*	3.8	87	78	65	18	6	8	4.2	0.62	121	948
			1.73	93†	3.4	77	72	65	—	4	6	3.3	—	—	929
2	57	Normal		68	2.0	98	90	80	10	4	7	2.5	0.16	62	1875
			1.92	78	2.4	90	82	74	—	0	5	2.7	—	—	1422
3	23	Normal		75	4.2	102	92	80	15	2	10	5.5	0.74	48	884
			1.98	88	4.0	95	85	76	—	0	—	4.8	—	—	1475
4	20	Normal		60	3.0	120	110	87	14	6	10	4.6	0.33	54	1503
			1.95	55	3.0	110	105	82	10	4	8	4.2	0.24	27	1434
5	20	Normal		80	3.4	110	88	74	—	—	—	4.8	—	—	1061
			1.95	81	3.6	100	78	60	—	—	—	4.6	—	—	888
6	37	Grade II basal		65	3.4	110	100	85	18	4	8	4.8	0.46	128	1285
		systolic murmur	1.83	82	3.7	100	92	75	14	2	6	4.7	0.48	94	1085
7	27	Grade I basal		72	2.7	95	77	60	14	2	12	3.3	0.50	34	1320
		diastolic murmur	1.73	78	2.5	90	66	45	—	0	—	2.8	—	—	1222
8	20	Atrial septal		70	2.2	95	88	80	20	10	10	2.6	0.89	206	1815
		defect, small	1.76	70	2.0	90	80	74	—	—	—	2.3	—	—	1929
9	22	Basal systolic		80	4.3	118	105	82	15	2	11	6.6	0.76	42	1128
		murmur	1.73	100	3.5	120	99	82	10	0	4	5.4	0.38	79	1306
10	27	Functional		90	3.7	116	97	85	17	5	12	5.5	0.59	68	1336
		systolic murmur	1.58	109	3.4	89	79	75	—	0	—	3.8	—	—	1171
Averages				73	3.3	105	93	78	16	4	9	4.4	0.56	87	1315
28.7			1.81	83	3.2	96	84	71	11	1	6	3.9	0.36	66	1290
Change (%)					—3.8	—9	—9	—9				—10	—36	—24	—2

*Before nitroglycerin.
†After nitroglycerin.

showed no significant change following nitroglycerin. All parameters of brachial arterial pressure were reduced an average of 9 per cent over the control values. Left ventricular work averaged 4.4 Kg.M./min./M^2 and changed insignificantly to 3.93 following nitroglycerin. Pulmonary arterial pressure averaged 16 mm. Hg in 3 patients and dropped to 11 mm. Hg following nitroglycerin. Pulmonary capillary wedge pressure averaged 9 mm. Hg at rest and fell to 6 mm. Hg in 8 observations. Right atrial mean pressure averaged 4 mm. Hg and decreased to 1 mm. Hg following nitroglycerin. Right ventricular work and pulmonary vascular resistance were satisfactorily measured in only 3 studies. Although they both decreased, no significance was attached in so small a group. Systemic vascular resistance showed no consistent or significant change.

Cardiac rates increased from 73 to 83 beats per minute with a 1.8 second lengthening of systole per minute and a reciprocal shortening in diastole per minute.

Coronary Hemodynamic Changes (Table 2). Coronary blood flow as measured per 100 Gm. of left ventricular muscle per minute averaged 66 ml. at rest and increased 63 per cent

TABLE 2.—*Effect of Nitroglycerin on the Coronary Circulation*

Patient	Cycle duration (sec./min.)		Coronary vascular resistance (dyne sec. cm.$^{-5}$)		Estimated left ventricular weight (Gm.)	Coronary flow (ml./min.)		Oxygen consumption (ml.)				Left ventricular work (Kg.M./min.)		Left ventricular efficiency (%)	
	Systole	Diastole	Mean	Diastolic		Per 100 Gm.	Per left ventricle	Per 100 Gm./min.	Per left ventricle/min.	Per 100 Gm./systolic second	Per systolic second/Kg.M. work	Per M.^{2} (body surface area)	Total	Per 100 Gm.	Total
1	22.4*	37.6	89‡	61‡	138.0	70	96	7.0	9.7	.31	.073	4.2	7.3	29	37
	28.0†	32.0	54	35		105	145	10.2	14.1	.37	.139	3.3	5.7	15	20
2	24.5	35.5	156	109	167.4	46	76	5.9	9.9	.24	.095	2.5	4.8	20	24
	24.9	35.1	77	54		85	142	11.4	19.2	.46	.166	2.7	5.3	11	13
3	24.0	36.0	103	72	183.0	71	130	10.1	18.5	.42	.075	5.5	11.0	26	29
	28.3	31.7	63	39		107	196	15.0	27.5	.53	.108	4.8	9.6	15	17
4	19.2	40.8	146	105	176.0	60	105	6.5	11.4	.34	.072	4.6	9.1	35	39
	18.5	41.5	100	71		84	147	9.2	16.2	.50	.116	4.2	8.3	22	25
5	25.6	34.4	106	51	176.0	66	116	9.2	16.2	.36	.074	4.8	9.4	25	28
	25.9	34.1	69	30		90	158	11.9	21.0	.47	.101	4.6	9.0	18	21
6	23.5	36.5	123	84	154.5	65	100	8.1	12.5	.35	.072	4.8	8.9	28	34
	25.4	35.6	85	55		82	126	9.4	14.4	.37	.077	4.7	8.7	24	29
7	27.4	32.6	96	55	141.3	63	89	8.5	12.0	.31	.094	3.3	5.7	18	23
	28.1	31.9	54	26		97	137	12.6	17.8	.45	.155	2.8	4.9	11	14
8	25.2	34.8	108	76	140.4	65	91	7.5	10.5	.30	.111	2.6	4.7	17	22
	25.2	34.8	49	35		130	182	16.6	23.3	.66	.285	2.3	4.0	7	8
9	25.6	34.4	102	45	144.2	82	118	11.2	16.2	.44	.066	6.6	11.4	28	34
	28.0	32.0	39	23		201	290	28.0	40.3	1.0	.180	5.4	9.4	9	25
10	27.0	33.0	114	65	116.0	67	79	9.0	10.5	.33	.059	5.5	8.7	29	40
	30.0	30.0	67	42		93	109	11.4	13.2	.38	.097	3.8	6.1	16	14
Average															
	24.4	35.6	114	73		66	100	8.3	12.7	.34	.079	4.4	8.1	26	29
	26.2	33.8	66	41		108	164	13.6	20.7	.53	.143	3.9	7.1	13	18
Change (%)															
	+6.9	—5	—42	—44		+63	+63	+63	+63	+56	+81	—10	—12	—50	—38

*Before nitroglycerin.
†After nitroglycerin.
‡=10^3.

to a value of 108 ml./100 Gm./min. This increase in flow was accomplished by a 42-per cent reduction in coronary vascular resistance.

Changes in Myocardial Gaseous Metabolism (Table 3). Coronary venous blood had an average oxygen content of 5.3 volumes per cent at rest, a saturation of 29 per cent, and oxygen tension of 19 mm. Hg. There were no significant changes in these values following the administration of nitroglycerin. Coronary venous carbon dioxide content averaged 53.7 volumes per cent and partial pressure 54 mm. Hg and did not change after nitroglycerin.

Extraction of oxygen and production of carbon dioxide remained unaltered.

Myocardial oxygen utilization at rest was 8.3 ml./100 Gm./min. and increased to 13. ml./100 Gm./min. (table 2). This increase in myocardial oxygen consumption paralleled the increased coronary flow, while oxygen ex

action remained fixed. Although oxygen nsumption increased, there was no change left ventricular work per minute. Consequently, left ventricular efficiency per 100 m., which was 26 per cent at rest, decreased 13 per cent with nitroglycerin. Column 1, table 2, reveals that the oxygen consumption per second of systole was 0.34 ml. at rest, ut increased to 0.53 following nitroglycerin. When this oxygen consumption was then expressed as ml. per systolic second per Kg.M. f work (column 12) the value nearly doubled rom a normal figure of 0.079 ml. at rest to 143 with nitroglycerin. This indicated that hanges in oxygen consumption were not related solely to changes in hemodynamics.

Discussion

Basic Action of Nitroglycerin. An agent which acts as a pure vasodilator does not alter the metabolism of the organ under study. If flow to the organ is increased through lowering of regional vascular resistance, then oxygen extraction and carbon dioxide removal per ml. of blood are correspondingly decreased. Hydralazine for example, has such an action on the coronary circulation: when flow increased, oxygen extraction decreased as evidenced by an increased coronary venous oxygen content, and cardiac oxygen consumption remained unaltered.[21]

Previous animal experiments have revealed varying reactions to nitroglycerin. Essex et al.[4] and Boyer and Green[5] showed an increase in coronary flow, but did not measure cardiac work or oxygen consumption. Foltz et al.[22] demonstrated a 12-per cent decrease in cardiac oxygen extraction during the first minute following a single 0.6-mg. dose of nitroglycerin intravenously in the dog, but did not measure cardiac work or oxygen consumption. Smaller doses had no such effect but did accelerate the heart and cause a small decrease blood pressure. Eckstein and co-workers[7] injected nitroglycerin directly into a coronary tery in 3 dogs. They found a 25-per cent crease in flow in 2 of 3 and an unchanged ygen consumption, but cardiac work was t measured. Sarnoff and associates in the isolated dog heart with fixed work and heart rate, showed that nitroglycerin acted as a "pure dilator" with decreased arteriovenous oxygen extraction as coronary flow increased.[8] In our own studies of the intact dog under varying anesthetic agents, when nitroglycerin was given as a constant intravenous infusion to the point of constant hypotension (at least 20 per cent below control value) we could not consistently demonstrate either coronary dilatation or decreased oxygen extraction; nevertheless a decrease in cardiac efficiency was always seen.[23] The difference between our findings and those of others remains unexplained.

Table 3.—*Action of Nitroglycerin on Myocardial Gaseous Metabolism*

Patient	Coronary sinus					Coronary arteriovenous difference (vol. %)	
			Gas tensions				
	O_2 content (vol. %)	CO_2 content (vol. %)	Oxygen (mm. Hg)	Carbon dioxide (mm. Hg)	O_2 saturation (%)	Oxygen	Carbon dioxide
1	4.0*	51.9	18	51	27	9.7	—
	4.0†	53.3	18	51	27	9.7	—
2	4.6	53.6	17	47	26	12.9	6.0
	4.0	54.3	16	51	23	13.5	6.3
3	5.0	—	—	—	25	14.3	—
	5.2	—	—	—	26	14.1	—
4	5.6	51.2	20	47	32	10.8	5.5
	5.0	51.7	20	59	28	11.0	6.5
5	4.8	55.0	17	51	25	14.0	7.1
	5.5	57.6	20	64	29	13.3	9.0
6	4.9	52.9	22	46	27	12.5	11.2
	6.0	50.0	24	49	33	11.4	9.0
7	3.9	59.2	14	48	22	13.5	10.7
	4.0	57.9	18	59	23	13.0	—
8	6.9	56.2	—	—	36	11.5	12.8
	5.5	54.8	19	50	29	12.8	9.3
9	6.3	57.0	22	59	33	13.7	9.6
	6.2	55.7	21	57	34	13.8	8.3
10	7.1	46.0	—	30	38	11.8	9.5
	6.2	45.3	—	30	34	11.7	9.0
Averages							
	5.3	53.7	19	54	29	12.5	8.7
	5.2	53.4	20	53	29	12.4	8.1

*Before nitroglycerin.
†After nitroglycerin.

The presently reported studies in man would indicate that myocardial oxygen consumption is increased during the administration of nitroglycerin. This is based on the fact that coronary flow increased by 63 per cent while the oxygen extraction remained unchanged. Coronary venous oxygen samples drawn at various times from 1 to 10 minutes after sublingual administration of nitroglycerin did not increase in content over the control value.

An alternative explanation of the experimental findings is a redistribution of blood flow within the myocardium, such that there was shunting of blood via other venous channels than the coronary sinus, and that this blood had very little oxygen extracted from it (as with arteriovenous fistula). This would not explain the fact that while the coronary artery-coronary sinus difference for oxygen was unchanged, the same samples revealed a narrowed arteriovenous difference for nitrous oxide. This would confirm the presence of increased outflow of blood from that portion of left ventricle drained via the coronary sinus and that oxygen consumption of that portion of myocardium seemed increased.

This increase in oxygen utilization is not altogether surprising in the light of in vitro studies of the biochemical action of the nitrites.[24] Hunter has shown that the various nitrites increase oxygen utilization in a manner similar to dinitrophenol, namely, uncoupling of oxidative phosphorylation. The very same action which relaxes smooth muscles may affect cardiac muscle contraction.[25] Other stimuli are known to evoke greater increases in coronary blood flow than nitroglycerin.[8] The increase of coronary flow may be solely that demanded by the increased myocardial needs for oxygen under the influence of nitroglycerin.

While cardiac oxygen consumption was elevated, cardiac work remained unaltered: cardiac efficiency decreased. This change in efficiency was not attributable to increased heart rate [oxygen consumption was still increased when computed per second of contraction (table 2)],[9] or large increase in cardiac diastolic volume.[26]

Other Hemodynamic Changes Induced by Nitroglycerin. There was remarkably little change in cardiac work. Blood pressure fell slightly while output remained the same or increased slightly. These findings agree with Starr's early studies[27] but not with Wegria's ballistocardiographic findings of marked increase in output.[28] Eldridge reported similar observations on cardiac output and work, and also demonstrated that nitroglycerin modified the blood pressure response to exercise as well.[29]

Johnson et al.[30] recently reported that nitroglycerin lowered pulmonary arterial pressure. This pressure decrease may be attributed to a decrease in central blood volume,[26] and in the diastolic filling pressure of the 2 ventricles, presumably related to a loss of venomotor tone.[31] We have occasionally seen profound hypotension in the recumbent position when acute arterial bleeding of 100 ml. is superimposed on nitroglycerin administration. This severe hypotension is attended by a concomitant fall in cardiac output and an unchanged systemic resistance. It is quickly reversed by non-cardiotropic vasopressor agents.

Summary

In 10 normal or mild cardiac subjects, observations of coronary and systemic circulatory dynamics and myocardial gaseous metabolism were made before and after the administration of nitroglycerin. Following nitroglycerin, myocardial oxygen consumption increased. Presumably related to this increased oxygen demand, coronary flow increased, mediated by a lowered coronary vascular resistance. The increase in myocardial metabolism was associated with unchanged cardiac work and a fall in myocardial efficiency. These changes were considered consistent with in vitro observations of increased oxygen consumption induced by nitrites during oxidative phosphorylation.

In these patients, cardiac output was essentially unchanged, while blood pressures decreased minimally. There were, however, significant decreases in pulmonary artery, pulmonary wedge, and right atrial pressures suggesting a relaxation of venomotor tone

SUMMARIO IN INTERLINGUA

In 10 normal o levemente cardiac subjectos, observationes relative al dynamica circulatori coronari e systemic e al metabolismo gasose myocardial esseva facite ante e post le administration de nitroglycerina. Post nitroglycerina, le consumption myocardial de oxygeno esceva. Probabilemente in dependentia de le augmentate demanda de oxygeno, le fluxo coronari se intensificava, mediate per un plus basse resistentia del vasos coronari. Le augmento del metabolismo myocardial esseva associate con constantia del labor cardiac e un reduction del efficacia myocardial. Iste alterationes esseva considerate como congruente con observationes in vitro de augmentos del consumption de oxygeno inducite per nitritos durante le phosphorylation oxydative.

In iste patientes, le rendimento cardiac esseva essentialmente inalterate, durante que le tension sanguinee descendeva minimalmente. Tamen, il occurreva reductiones significative del tensiones pulmono-arterial, pulmonar a cuneo, e dextero-atrial. Isto pareva indicar un relaxation del tono venomotori.

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Medical Eponyms

By Robert W. Buck, M.D.

S **Curve of Ellis.** At a meeting of the Boston Society for Medical Improvement, October 13, 1873, Professor Calvin Ellis (1826-1883) of the Harvard Medical School discussed "The Line of Dulness in Pleuritic Effusion." His remarks were reported in the *Boston Medical and Surgical Journal* 90: 1314 (January 1) 1874.

"In a certain number of cases where the effusion is quite large, if an accurate line be drawn, the flatness will be found to describe a curve, gradually approaching the spine toward the base of the chest, having a space from one to three or more inches broad between the spine and the line of flatness. In this space, resonance will still be detected, and respiration heard. As the effusion increases, this line approaches nearer and nearer the spine, until the whole back becomes flat."

The attention of Dr. Ellis was called to the fact that Damoiseau had described a similar curve, and he said that until his attention had been called to this, he had not been aware that the point had been observed but that Damoiseau's description of this curve agreed with his observation.

His (first) article on "The Curved Line of Pleuritic Effusion" appeared in the *Boston Medical and Surgical Journal* 95: 689-697 (December 14) 1876. It consists of a series of case histories and several diagrams showing a curve on the posterior aspect of the thorax in the form of an *S*, whose tail begins at the vertical column and whose tip descends into the axilla towards the sternum. The text contains no description of the term. The term *S Curve of Ellis* was applied by Garland (cf. Garland's Triangle).

Effect of Nitroglycerin on the Coronary Circulation in Patients with Coronary Artery Disease or Increased Left Ventricular Work

By Richard Gorlin, M.D., Norman Brachfeld, M.D., Colin MacLeod, M.D., and Pierre Bopp, M.D.

Except for the electrocardiogram objective evaluation of the functional state of the coronary circulation in man is often difficult. The nature of the coronary circulation in the presence of known coronary insufficiency has not been evaluated. In this report, 17 patients were studied of whom 14 had angina pectoris. Observations were made of coronary blood flow and hemodynamics both at rest and following administration of nitroglycerin. The authors conclude that *resting* coronary flow is normal, but *cannot increase* further with dilators. They consider this phenomenon a consequence of prior exhaustion of the dilator capacity of the arterioles in compensation for the atherosclerotic obstruction of the coronary tree. The "fixed flow" concept is suggested as an objective means of detecting coronary insufficiency. Nitrites probably relieve pain in some manner other than general coronary dilatation.

UNTIL the present time few objective assessments[1] of the state of the coronary circulation have been made except for electrocardiographic and ballistocardiographic observations. In these studies correlation was possible only with clinical findings and postmortem observations. The electrocardiogram has been extremely helpful, particularly when it has indicated myocardial ischemia. As has been pointed out by many workers, however, it gives only indirect information concerning the state and adequacy of the coronary circulation.[2] Inadequate technics have limited the acquisition of knowledge about the functional state of the diseased coronary circulation in man. Physiologic principles have been freely applied to the understanding of other cardiac problems, particularly valvular heart disease[3] and congestive failure.[4] A similar physiologic approach to the coronary circulation would be of value.

In order to be detected by a test of physiologic function, disease of an organ system must be diffuse and often far advanced. The patchy distribution of the lesions of atherosclerosis has raised doubts that a uniform decrease in function of a given organ system always takes place. Nevertheless, it has been shown that patients with cerebral arteriosclerosis show a statistically lower cerebral blood flow per 100 Gm. of brain tissue than do normal subjects.[5] Despite the patchy distribution of the disease, there are apparently enough lesions to affect function. The coronary vessels show a somewhat similar pathologic picture. Pathologic studies conducted by many workers have demonstrated that these arteries seldom show a single vascular disturbance,[6-8] but more often demonstrate diffuse involvement of the entire coronary vascular tree with varying types of lesions, areas of narrowing, thrombosis, occlusion, etc., all leading to increased large vessel resistance to blood flow. The diffuseness of the disease process may affect measurable functions in 1 of 2 ways: decrease resting coronary flow and possibly myocardial oxygen consumption values, and thus differ from *normal* resting values, as was seen in cerebral arteriosclerosis; limit the vasodilator capacity of the coronary arteriolar bed and thus differ from the normal in the ability of the coronary circulation to deliver more blood upon demand. Such a de-

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TABLE 1.—*Clinical Evidence of Coronary Insufficiency*

Patient	Diagnosis	Angina pectoris	Nitroglycerin pain relief	Electrocardiogram	
				Rest	Exercise
Coronary artery disease					
1	Coronary artery sclerosis	Present	Partial	Ischemia	—
2	Coronary artery sclerosis	Present	Good	Ischemia + old myocardial infarction	—
3	Coronary artery sclerosis	Present	Good	Negative	Equivocal
4	Coronary artery sclerosis	Present	Good but slow	Depressed S-T segment in AVF	Abnormal
5	Coronary artery sclerosis	Present	Good	Inverted T wave, leads I, aV_L + precordial lead	—
6	Coronary artery sclerosis	Present	Partial	Left ventricular hypertrophy	Abnormal
7	Coronary artery sclerosis	Present	None	? old posterior myocardial infarction	Abnormal
Increased left ventricular work					
1	Mitral insufficiency	Present	Not used	Left ventricular hypertrophy	—
2	Mitral insufficiency	—	— —	Left ventricular hypertrophy	—
3	Mitral insufficiency	—	— —	Left ventricular hypertrophy	—
4	Aortic insufficiency	Present	Partial	Left ventricular hypertrophy	Abnormal
5	Aortic stenosis	Present	Not used	Coronary T waves—left ventricular hypertrophy	—
6	Aortic stenosis	Present	Partial	Left ventricular hypertrophy	—
7	Aortic insufficiency	Present	Partial	Left ventricular hypertrophy	Abnormal
8	Aortic stenosis old myoc. infarct.	—	— —	Left ventricular hypertrophy	—
9	Aortic stenosis + insufficiency	Present	Not used	Left ventricular hypertrophy	Abnormal
10	Aortic stenosis + insufficiency	Present	No relief	Left ventricular hypertrophy	—

crease in dilator capacity has been seen in cerebral vascular disease.[9]

To assess the above-mentioned physiologic consequences of vascular disease, observations were made at rest and following an agent alleged to increase coronary flow. In the preceding paper[10] nitroglycerin was shown to induce an increased coronary blood flow in normal or nearly normal individuals. This drug was used as the first coronary dila or agent in the abnormal patients because of he patients' familiarity with it and its simpli ty and relative safety. This report presents ob- servations in patients with either clinical c ro- nary artery disease or a chronically incre ed left ventricular work load. These 2 categ ies may be expected to challenge the vasodila ng capacity of the coronary vascular bed.

TABLE 2A.—*Effect of Nitroglycerin on the Pulmonary and Systemic Circulations in Patients with Coronary Artery Disease*

Patient	Age	Body surface area (M^2)	Heart rate per min.	Cardiac output (L./min./M^2)	Pressures (mm. Hg)						Ventricular work (Kg.M./min./M^2)		Vascular resistances (dyne sec. $cm.^{-5}$)	
					Brachial artery									
					Systolic mean	Mean	Diastolic mean	Pulmonary artery mean	Right atrial mean	Pulmonary capillary mean	Left	Right	Pulmonary	Systemic
			63*	2.5	130	105	90	—	—	—	4.1	—	—	2192
1	68	1.5	79†	1.7	105	90	85	—	—	—	2.3	—	—	2762
			77	3.5	100	87	80	—	—	—	4.6	—	—	1104
2	37	1.8	66	2.5	52	48	44	—	—	—	1.6	—	—	853
			75	2.9	102	85	82	—	—	—	3.8	—	—	1419
3	42	1.7	75	2.7	90	83	81	—	—	—	3.1	—	—	1488
			90	3.5	108	102	90	21	5	12	4.8	0.76	113	1280
4	54	1.8	97	3.4	100	95	88	16	—	8	4.3	0.70	104	1230
			81	2.7	122	107	98	—	—	—	4.4	—	—	2192
5	52	1.5	115	3.3	92	87	79	—	—	—	4.1	—	—	1449
			75	2.9	106	85	81	16	4	10	4.2	0.88	104	1840
6	51	1.6	56	2.8	92	75	71	14	2	8	3.5	0.60	106	1010
			88	3.5	134	95	90	23	3	15	6.1	0.94	110	1311
7	44	1.7	85	2.0	100	82	75	19	—	—	2.6	0.49	93	2220
Average														
			78	3.1	115	95	87	20	4	12	4.6	0.86	109	1620
	50	1.6	82	2.6	90	80	75	18	2	8	3.1	0.60	99	1573
Change (%)														
			+5	—16	—22	—16	—14	—10	—50	—33	—33	—31	—9	—3

*Before nitroglycerin.
†After nitroglycerin.

MATERIALS AND METHODS

Eighteen observations were made in 17 patients (table 1). Group I (the "coronary" group) consisted of 7 patients with coronary sclerosis and angina pectoris. Group II (the "work" group) consisted of 10 patients: 3 with mitral insufficiency, 4 with aortic stenosis, 3 with aortic insufficiency; 7 of the 10 had angina pectoris. All patients were classified in disability groups 3 or 4 according to criteria of the American Heart Association.

The methods utilized were described in the preceding paper.[10] In addition to right heart catheterization, left heart catheterization was performed in the patients with aortic valvular disease.[11] Valvular regurgitation in liters per minute was estimated by the method of Korner and Shillingford.[11, 12]

In patients 9 and 10 of group II the aortic valves were examined cinegraphically at autopsy. On the basis of calculated areas the volume of regurgitation was verified hydraulically.[13]

By means of formulas described elsewhere[13] left and right ventricular work were calculated as Kg.M./min./M^2 In aortic valvular disease left ventricular systolic mean pressure was used in the work calculation. This value was back calculated from the valve area calculated during the left heart catheterization[11, 13] using hemodynamics measured at the time of each of the 2 coronary flows. Cardiac outputs entering the work calculation in the patients with valvular insufficiency included both effective and regurgitant flows.[11]

Systemic and pulmonary resistances were calculated[11] as dyne sec. $cm.^{-5}$ Coronary vascular resistance, both mean and diastolic, and myocardial oxygen consumption were calculated as described previously.[10] Mechanical efficiency was calculated both per 100 Gm. and for the estimated total left ventricle,[10] in the coronary group. Because actual left ventricular weight was obviously much greater than the estimated values in subjects with electrocardiographic signs of hypertrophy, no calculated estimates were made in the "work" group. True left ventricular weights were obtained in patients 9 and 10 at autopsy.

TABLE 2B.—*Effect of Nitroglycerin on the Circulation in Patients with Coronary Artery Disease*

Patient	Cycle duration (sec./min.)		Coronary vascular resistance (dyne sec. cm.$^{-5}$)		Estimated left ventricular wt. (Gm.)	Coronary flow (ml./min.)		Oxygen consumption (ml.)				Left ventricular work (Kg.M./min.)		Left ventricular efficiency (%)	
	Systole	Diastole	Mean	Diastolic		Per 100 Gm.	Per left ventricle	Per 100 Gm./min.	Per left ventricle/min.	Per 100 Gm./systolic second	Per systolic sec./Kg.M. work	Per M.^{2} (body surface area)	Total	Per 100 Gm.	
1	19.0*	41	113§	88§	118	74	88	8.2	13.0	.43	.105	4.1	6.3	18	
	19.0†	41	94	81		76	90	7.8	12.1	.41	.178	2.3	3.5	11	
2	19.3	40.7	74	61	126	94	118	10.4	13.1	.54	.120	4.6	8.3	21	
	21.8	38.2	76	62		48	61	5.3	6.6	.25	.156	1.6	2.9	14	
3	24.0	36.0	75	58	143	90	129	7.7	11.0	.32	.085	3.8	6.3	23	
	22.5	37.5	75	61		88	126	7.2	10.3	.32	.104	3.1	5.1	20	
4	22.7	37.3	96	70	156	85	133	10.5	16.4	.46	.100	4.8	8.7	22	
	25.2	34.8	97	69		78	122	9.3	14.0	.36	.080	4.3	7.7	23	
5	27.3	32.7	92	61	108	93	100	10.8	11.5	.39	.089	4.4	6.4	20	
	30.5	29.5	81	48		85	92	11.1	10.6	.31	.076	4.1	5.9	20	
6‡	21.0	39.0	124	102	125	55	69	5.1	6.4	.24	.058	4.2	6.7	40	
	16.8	43.2	151	136		40	50	3.5	4.4	.21	.059	3.5	5.5	49	
7	23.8	36.2	92	70	147	81	119	10.3	15.0	.43	.070	6.1	10.1	29	
	20.2	39.8	95	77		69	101	8.1	12.0	.40	.156	2.6	4.3	15	
Average															
	22.4	37.6	95	73	132	82	108	9.0	12.0	.40	.089	4.6	7.5	25	
	22.3	38.0	95	77		69	92	7.5	10.0	.32	.115	3.1	4.9	22	
Change (%)															
	—0.5	+6	0	+5		—16	—15	—17	—17	—20	+23	—33	—34	—12	

*Before nitroglycerin.

†After nitroglycerin.

‡This patient had left ventricular hypertrophy by EKG, probably secondary to the underlying coronary vascular disease. This would seem to explain the apparently low coronary flow and high coronary resistance per 100 Gm.

§Times 10^3.

RESULTS

General Hemodynamic Changes (Tables 2A, 3A). Effective cardiac output averaged 3.3 L./min./M.^{2} and in contrast to the unchanged flows in the normal group, decreased 15 per cent to 2.8 L./min./M.^{2} after nitroglycerin. Brachial arterial systolic mean blood pressures decreased 20 per cent while mean and diastolic mean pressure fell 16 and 15 per cent respectively. Left ventricular work decreased 30 per cent over the resting value, while in the "normal" patients work did not change.

Following nitroglycerin, pulmonary arterial and capillary pressures and right atrial pressure decreased from 50 to 62 per cent below the control values, the fall being greater the higher the initial pressure. Right ventricular work, measured in only 6 cases, showed a decrease. Pulmonary vascular resistance did not change in 6 patients studied. Systemic vascular resistance showed no change in any group.

Cardiac rate increased only slightly with insignificant changes in systolic and diastolic periods.

TABLE 2C.—*Effect of Nitroglycerin on Myocardial Gaseous Metabolism in Patients with Coronary Artery Disease*

Patient	Coronary sinus					Coronary arteriovenous difference (vol. %)	
			Gas tensions				
	O_2 content (vol. %)	CO_2 content (vol. %)	Oxygen (mm. Hg)	Carbon dioxide (mm. Hg)	O_2 saturation (%)	Oxygen	Carbon dioxide
1	5.8*	62.5	20	52	33	11.1	9.4
	6.3†	60.3	22	57	35	10.2	7.4
2	7.1	53.8	20	49	35	11.9	9.2
	7.9	50.9	23	50	38	11.1	9.0
3	6.9	50.0	25	47	42	8.6	7.8
	7.3	48.7	25	44	47	7.6	5.9
4	5.0	55.8	17	49	28	12.6	7.2
	5.1	56.1	18	49	29	11.9	11.5
5	5.8	59.8	21	59	32	11.5	10.8
	4.1	57.3	24	57	38	13.1	9.7
6	5.8	63.0	20	51	36	9.3	11.8
	5.6	60.2	21	48	36	8.7	10.0
7	4.2	52.9	16	51	21	12.7	13.0
	4.7	49.9	16	46	24	12.2	8.2
Average	5.8	56.8	20	51	33	11.1	9.9
	5.9	54.8	21	50	35	10.8	8.8

*Before nitroglycerin.
†After nitroglycerin.

Coronary Hemodynamics (Tables 2B, 3B). Coronary flow averaged 82 ml./100 Gm./min. in the "coronary" group and 77 ml./100 Gm./min. in the "work" group—both figures larger than the resting normal value of 66 ml./100 Gm./min. Following nitroglycerin, flow decreased 16 per cent in the "coronary" patients and was essentially unchanged in the "work" group, whereas in the "normal" subjects flow increased 63 per cent. Coronary resistance did not change (−4 and 0 per cent) significantly in either the "work" or the "coronary" groups except for 2 patients (9 and 12) in the "work" group.

Myocardial Gaseous Metabolism (Tables 2B and 2C and 3B and 3C). Coronary venous blood varied in oxygen content from 3.2 to 7.9 volumes per cent. Similarly, oxygen saturation ranged from 18 to 42 per cent and tension averaged 20 mm. Hg. There were no consistent changes in any values after nitroglycerin, including samples drawn within the first 2 minutes after administration. Similarly, there were no major deviations from normal in coronary venous carbon dioxide content, partial pressure of carbon dioxide, or pH. Extraction of oxygen and production of carbon dioxide remained essentially unchanged.

The myocardial oxygen utilization was slightly higher in both groups compared to the normal. Following nitroglycerin, oxygen consumption decreased or remained unchanged.

Resting myocardial efficiency per 100 Gm. was slightly decreased in the "coronary" group as compared to the normal group (except 6). Efficiency per 100 Gm. of left ventricle was normal or greater than normal in the "work" group. The presence of increased muscle mass in the latter group, however, gives a false picture of myocardial efficiency.[1] This was best illustrated when *total* efficiency was calculated for patients 9 and 10 in whom actual left ventricular weight was known: whereas efficiencies *per 100 Gm.* of left ven-

TABLE 3A.—*Effect of Nitroglycerin on the Pulmonary and Systemic Circulations in Patients with Increased Left Ventricular Work*

Patient	Age	Body surface area ($M.^2$)	Heart rate per min.	Cardiac output (L./min.) Total per $M.^2$*	Cardiac output (L./min.) Effective† per $M.^2$	Pressures (mm. Hg) Brachial artery Systolic mean‡	Brachial artery Mean	Brachial artery Diastolic mean	Pulmonary artery mean	Right atrial mean	Pulmonary capillary mean	Ventricular work (Kg.M./min./$M.^2$) Left	Ventricular work (Kg.M./min./$M.^2$) Right	Vascular resistances (dyne sec. $cm.^{-5}$) Pulmonary	Vascular resistances (dyne sec. $cm.^{-5}$) Systemic
			68§	7.0	3.3	120	105	88	23	8	19	10.9	0.60	54	14
1	20	1.77	83¶	5.0	2.4	100	90	77	15	4	10	6.2	0.35	94	16
			80	6.6	3.0	94	87	73	30	5	25	8.0	1.0	91	15
2	30	1.45	90	6.3	3.0	85	70	64	—	3	—	6.9	—	—	12
			130	4.0	2.8	120	110	100	—	—	—	6.2	—	—	20
3	44	1.54	73	2.3	1.7	85	75	67	15	1	10	2.5	—	152	22
			90	5.8	1.9	125	90	80	32	6	22	9.5	0.67	254	22
4	36	1.65	92	5.8	2.0	95	78	65	—	—	—	7.1	—	—	18
			83	3.9	—	90	82	74	32	5	24	9.7	1.4	94	96
5	30	1.74	100	3.9	—	84	77	69	—	—	—	8.1	—	—	96
			80	2.7	—	98	82	73	33	3	25	5.5	1.1	145	14
6	41	1.63	110	3.2	—	67	67	62	—	—	—	5.5	—	—	10
			91	5.1	4.4	125	88	75	17	5	12	11.7	0.72	49	86
7	48	1.85	98	3.7	3.0	112	88	77	12	0	5	6.4	0.49	100	12
			65	3.1	—	105	100	92	—	—	—	6.2	—	—	13
8a	40	1.92	81	2.4	—	100	90	83	—	—	—	3.1	—	—	15
			93	3.0	—	103	93	88	—	—	—	4.0	—	—	12
8b	40	1.92	83	2.0	—	58	53	50	—	—	—	1.6	—	—	11
			71	7.6	4.1	111	81	72	—	—	—	17.7	0.91	56	15
9	54	1.90	80	6.7	3.6	90	72	63	—	—	—	15.3	—	—	15
			90	9.0	5.0	110	95	85	16	—	12	20.5	0.98	40	84
10	24	1.88	96	9.0	5.0	105	85	85	13	—	9	19.6	0.88	40	75
Average‡			86	5.3	3.5	109	92	82	26	5	20	10.0	0.90	98	143
	37	1.75	90	4.6	2.9	89	77	69	14	2	9	7.5	0.57	96	139
Change (%)			+5	—13	—14	—18	—16	—15	—47	—62	—57	—25	—37	—2	—3

*"Total" refers to total minute volume including regurgitant flow.

†"Effective" is that portion delivered to peripheral tissues.

‡Left ventricular systolic pressures not shown in this table were measured at left heart catheterization and used in calculation of total left ventricular work.

§Before nitroglycerin.

¶After nitroglycerin.

8a=Preop. aortic valvuloplasty.

8b=Postop. aortic valvuloplasty.

tricle were 117 and 84 per cent respectively, the efficiencies for the total left ventricle were 43 and 34 per cent respectively. A further decrease in efficiency occurred after nitroglycerin in both groups. In tables 2B and 3B are various derivations of oxygen consumption in relation to the hemodynamic activity of the heart. Oxygen consumption per second of systole* was increased over resting values or was unchanged following nitroglycerin in both groups. When expressed in terms of consumption per Kg

*This calculation adjusts for the effects of cardiac rate on oxygen consumption.

TABLE 3B.—*Effect of Nitroglycerin on the Coronary Circulation in Patients with Increased Left Ventricular Work*

	Cycle duration (sec./min.)		Coronary vascular resistance (dyne sec. cm.$^{-5}$)			Coronary flow (ml./min.)		Oxygen consumption (ml.)				Left ventricular work (Kg.M./min.)		Left ventricular efficiency (%)	
	Systole	Diastole	Mean	Diastolic	Estimated left ventricular weight (Gm.)	Per 100 Gm.	Per left ventricle	Per 100 Gm./min.	Per left ventricle/min.	Per 100 Gm./systolic second	Per systolic second/Kg.M. work	Per M.^{2} (body surface area)	Total	Per 100 Gm.	Total
1	22.0*	38.0	91‡	63‡		85		10.5		.48	.114	10.9	19.3	50	
	26.0†	34.0	73	47		94		12.0		.46	.131	6.2	10.9	28	
2	23.0	37.0	103	71		67		7.5		.35	.116	8.0	11.5	51	
	21.6	38.4	71	55		78		8.4		.39	.144	6.9	9.9	39	
3	24.7	35.3	106	74		83		13.9		.56	.122	6.2	9.6	21	
	16.8	43.2	96	83		62		9.6		.57	.301	2.5	3.8	12	
4	23.4	36.6	84	60		86		13.0		.56	.058	9.5	15.6	35	
	23.5	36.5	77	54		79		18.0		.52	.068	7.1	11.7	19	
5	26.0	34.0	72	47		95		12.2		.48	.047	9.7	16.8	38	
	30.0	30.0	73	44		84		10.9		.36	.047	8.1	14.0	36	
6	22.4	37.6	90	69		71		10.1		.45	.082	5.5	8.9	26	
	28.6	31.4	95	61		56		7.3		.26	.046	5.5	8.9	36	
7	23.2	36.8	92	65		76		9.6		.41	.037	11.7	21.6	59	
	26.5	33.5	102	66		69		9.6		.36	.056	6.4	11.8	32	
8a	25.3	34.7	124	88		64		9.3		.36	.057	6.2	11.3	32	
	27.7	32.3	110	73		65		8.9		.32	.089	3.1	7.6	20	
8b	23.2	36.8	129	104		57		6.5		.28	.070	4.0	7.6	29	
	23.7	36.3	141	105		30		3.7		.16	.110	1.6	3.0	20	
9	23.6	36.4	103	75		62	320	7.3	38	.30	.017	17.7	33.6	117	43§
	26.0	34.0	79	52	520	73	380	9.4	49	.36	.024	15.3	29.2	79	29
10	22.5	37.5	85	63		89	400	11.8	53	.52	.025	20.5	38.5	84	35§
	24.0	36.0	74	59	499	91	409	11.8	53	.49	.025	19.6	36.8	80	34
Average															
	23.0	36.4	94.4	70.3		77		10.2		.43	.065	10.0	17.7	49	
	24.9	35.5	90.4	65.4		71		9.9		.39	.101	7.5	13.4	36	
Change (%)															
	+8	—3	—4	—7		—8		—3		—9	+55	—25	—24		

*Before nitroglycerin.
†After nitroglycerin.
‡Times 10^2.
§All calculations based on left ventricular weights and aortic valve areas measured directly at postmortem examination.

work* oxygen expenditure per 100 Gm. systolic second was increased in the "coronary" group as compared with the normal. In the "work" group oxygen consumption per Kg.M. was normal per 100 Gm. and therefore increased in terms of total heart weight.[1] Oxygen consumption per Kg.M. increased after nitroglycerin in both groups.

*This calculation derives the oxygen cost of a kilogram meter of work after oxygen cost has been adjusted for time spent in construction.

DISCUSSION

Validity of Method

The validity of the nitrous oxide flow method in the presence of obstructive vascular

TABLE 3C.—*Effect of Nitroglycerin on Myocardial Gaseous Metabolism in Patients with Increased Left Ventricular Work*

	Coronary sinus					Coronary arteriovenous difference (vol. %)	
			Gas tensions				
Patient	O_2 content (vol. %)	CO_2 content (vol. %)	Oxygen (mm. Hg)	Carbon dioxide (mm. Hg)	O_2 saturation (%)	Oxygen	Carbon dioxide
1	6.0*	53.1	24	46	32	12.3	9.3
	6.0†	50.0	20	42	36	12.7	7.4
2	6.0	42.7	22	51	33	11.5	8.0
	5.5	48.3	20	41	31	10.7	5.4
3	3.7	58.8	12	48	18	16.7	13.8
	3.9	55.4	13	45	20	15.5	12.3
4	4.6	55.4	—	—	24	15.3	9.3
	4.7	53.6	—	—	24	15.6	12.0
5	4.4	—	—	—	—	12.8	—
	4.2	—	—	—	—	13.0	—
6	3.5	57.2	12	43	19	14.3	12.0
	4.3	55.7	14	40	23	13.1	11.5
7	6.2	56.7	18	46	32	12.5	10.0
	4.9	56.2	16	45	26	13.9	8.3
8a	4.5	56.7	17	55	24	14.4	9.6
	5.0	56.0	19	56	27	13.7	—
8b	4.4	52.9	17	45	27	11.3	5.7
	3.3	53.1	13	41	20	12.3	9.7
9	5.7	60.0	18	52	30	11.8	12.9
	6.8	59.0	20	55	33	12.0	10.0
10	5.8	55.7	20	56	30	13.3	9.6
	6.1	53.8	19	48	31	13.1	10.3
Average							
	5.0	54.9	18	49	27	13.3	10.0
	5.0	54.1	17	46	27	13.4	9.7

*Before nitroglycerin.
†After nitroglycerin.

disease has been questioned. The major criticisms have been that functioning tissue may be inadequately perfused or that much of the blood may perfuse nonfunctioning scar tissue in a diseased organ. Poor regional perfusion could conceivably interfere with uptake of nitrous oxide by myocardium. Full myocardial saturation with gas was revealed, however, by the nearly identical concentration obtained from arterial and coronary venous blood drawn after 10 minutes' breathing of nitrous oxide. At this point, sampling of flow during nitrous oxide desaturation was begun. The proponents of the method[11, 14-17] have pointed out that when the nitrous oxide was removed from the blood (arteriovenous difference) this represented extraction by perfused tissue. If the coronary sinus were to receive venous blood from many fibrous nonmuscular portions of the heart, then nitrous oxide and oxygen present in arteries entering these areas would be removed to only a minimal degree compared to that taken up in muscle tissue. As a consequence "contaminated" curves and abnormally narrow arteriovenous differences for nitrous oxide and

or oxygen would be obtained and flows so calculated would be higher than normal. No such observations have been made in this study, indicating that sampling of perfused saturated muscle was adequate. Because flow was measured for a representative 100 Gm. of the perfused left ventricle, and because the characteristics of the sampling were no different from normal, either with respect to saturation or shape of the arteriovenous curve, it can be assumed that flow was measured primarily for perfused viable left ventricular muscle. Moreover, each patient served as his own control and findings could be duplicated in 1 patient on 2 separate occasions. Whatever the cause, a striking difference was shown between the response of the normal and the abnormal circulations.

These findings were confirmed by an independent method, the transcoronary circulation time.[18] I^{131} serum albumin was injected intravenously as a tracer substance and its passage was detected first by a surface scintillation counter placed over the precordium and secondly on arrival at the coronary sinus. Since the isotope was contained completely within the vascular tree, this circulation time could independently check on the direction of flow. Table 4 shows that coronary circulation time decreased following nitroglycerin in normal subjects, but remained unchanged or actually increased in abnormal patients.

TABLE 4.—*Transcoronary Circulation Time (TCT)*

	Patient	Nitroglycerin	Arrival time (sec.) Left heart (LH)	Arrival time (sec.) Net cor. venous (CV)*	TCT (LH-CV)	Cor. flow (ml./100 Gm./min.)
Normal	No. 1	a	13	22	9.0	70
		p	8	13.5	5.5	105
	No. 9	a	6.5	13	6.5	82
		p	7.5	11	3.5	201
Abnormal	"Coronary" group no. 5	a	10	15	5	93
		p	9	13	4	85
	"Work" group no. 1	a	13	24	11	85
		p	10	21	11	94

*Net coronary venous arrival time=time corrected for catheter-to-counter time delay.
a=Before.
p=After.

Hemodynamic Changes

General Circulatory Dynamics. That cardiac work would decrease in the abnormal patients while remaining unchanged in normal ones, would suggest that the decrease in work is not due primarily to loss of venomotor tone with a resulting fall in cardiac filling pressure, as this latter change occurred in both groups of patients. Ziffer and co-workers[19] showed that sodium nitrite caused cardiac output to fall in normal subjects and to rise in patients with congestive failure when venous pressure decreased; they believed this to be an expression of Starling's law. Our patients with heart failure, on the other hand, showed a striking decrease in work after nitroglycerin. This would seem most consistent with the concept that nitroglycerin affects circulatory function via the myocardium as well as via the vessels peripherally. In fact, various workers have commented on the severe and occasionally dangerous hypotensive effects of nitroglycerin in coronary patients.[20]

Pulmonary venous pressure decreased more in those with an initially elevated pressure. This probably depended on the shape of the veno-atrial volume elasticity curve.[21, 22]

Coronary Circulatory Dynamics. Resting values for coronary blood flow and myocardial oxygen consumption per 100 Gm. of left ventricular muscle were somewhat increased in the "coronary" and "work" groups as compared to our "normal" patients. That these values were normal or greater would be expected, since cardiac work performance at rest is the same in both normal subjects and in our patients with coronary inadequacy. Cardiac muscle has little potential for oxygen storage,[23] is ill-equipped for anaerobic glycolysis as a major energy source[24] and oxygen is almost maximally extracted from each milliliter of blood passing through the coronary capillary bed.[25] All these factors make the coronary system a flow-sensitive system.[25]

This situation differs from that in patients with cerebral arteriosclerosis whose oxygen consumption per 100 Gm. of brain tissue is decreased and therefore whose flow is reduced. In addition, cerebral oxygen extraction is so small that a large oxygen reserve remains available even if cerebral flow were restricted.[17]

When nitroglycerin was given, coronary blood flow failed to increase normally and, in fact, decreased in some patients. Coronary vascular resistance was found to be virtually fixed. Lombardo and co-workers reported similar findings in a single case of angina pectoris subjected to exercise.[26] The increase in coronary flow in their patient directly paralleled an increase in blood pressure with a fixation of the coronary vascular resistance (presumably due to coronary artery disease).

With a fixed coronary arteriolar resistance and fixed flow, oxygen supply to the heart is necessarily limited unless flow is augmented by an increase in perfusion pressure, or the last 0.02 to 0.03 ml. of oxygen are extracted per ml. of blood. A fixed coronary resistance was found in 2 clinical conditions. The first to be considered is coronary vascular disease. These patients had angina pectoris by the usual criteria (table 1). In these individuals, pathologic examination would undoubtedly demonstrate obstruction of at least 2 coronary arteries.[7] Hypoxia following obstruction of a large artery results in the opening up of collateral circulation.[27] This situation differs from that in an ischemic extremity, where deficient flow can readily be compensated for by increased oxygen extraction. The lack of such potential in the heart equates decrease in flow with production of hypoxia—all other factors remaining the same. It would appear that hypoxia had already produced near maximal coronary vasodilatation in this group. The reserve for further vasodilatation was nearly exhausted. Physiologically, as well as pathologically, the disease of the coronaries was diffuse.

The second clinical group with fixed coronary arteriolar resistances were those patients with a long-standing, marked increase in left ventricular work. Seven patients had aortic stenosis or insufficiency; 3 had severe mitral insufficiency with an unusually high flow load. In this group, total coronary blood flow was increased at rest merely to meet increased work demands of the hypertrophic ventricle. Experimental studies dating from the turn of the century have indicated that delivery of increased pressure or flow demands and increased myocardial oxygen and substrate consumption.[28] Studies in man have shown a direct relationship between myocardial oxygen consumption and work performed.[29] It would appear reasonable that, if the work load were large enough and hypertrophy excessive, at some point the capacity of the vascular bed to dilate to meet the need for oxygen might be almost fully utilized even at rest. The limiting point of course would be brought on sooner if intrinsic coronary arterial disease were already present.

The interplay of work, hypertrophy, and vascular disease is illustrated by the findings in 2 patients not in this series. In both a coronary reserve could be demonstrated despite serious heart disease.

The first patient was a woman of 36 with aortic insufficiency. Blood pressure was 150/65; she had neither cardiac symptoms nor left ventricular hypertrophy. Left ventricular work at rest was twice the normal, yet coronary flow (already elevated at rest) increased 40 per cent with nitroglycerin.

The second patient was a man of 51 with surgically proved aortic stenosis (0.5 cm.^{2}). He had adjusted to an extremely low cardiac output in the absence of cardiomegaly or gross congestive failure. He did not have angina pectoris. Work output was low normal and coronary flow increased 45 per cent with nitroglycerin. The resting need for oxygen, and therefore coronary flow, was normal and reserve for further dilatation remained.

Similar studies have been done in the experimental animal by production of coronary stenosis. Gregg demonstrated that with progressive arterial narrowing coronary flow could remain unchanged up to a certain point by a concomitant lowering of coronary arteri-

lar resistance.[27] These findings were expressed in another way by Case and coworkers, who showed in the dog that, with progressive anemia, the coronary bed could be made to deliver up to 4 times the normal resting flow and thus maintain oxygen supply.[30] The decreased oxygen-carrying capacity of the blood was compensated for by an increased coronary flow resulting from lowered coronary resistance. As anemia became progressively worse, coronary dilatation became maximal. Bleeding beyond this point depressed the ventricular function curve and led eventually to congestive failure and the death of the animal. In the presence of experimental coronary stenosis, dilatation was less effective in increasing coronary flow and depression of ventricular performance occurred more quickly.

The number of arterioles present in the human heart probably does not increase with age, and if the myocardium hypertrophies the number of capillaries per mm.^{2} is actually decreased.[31] Therefore, without new blood vessel growth there is a finite limit to the degree of vasodilatation that may take place. Pathologic studies indicate that coronary sclerosis begins early in life and usually involves the main coronary arteries[6-8, 32, 33] long before cardiac complaints ever appear. This undoubtedly decreases the theoretically available dilating capacity of the human coronary bed and makes it difficult to estimate absolute maximal coronary flow in the so-called normal adult.

Studies with nitroglycerin indicate that this stimulus increases coronary flow by at least 50 per cent in normal subjects, but hardly at all in the "coronary" and "work" groups. This is presumably due to prior "exhaustion" and the inability of an already maximally dilated arteriolar bed to respond with further dilatation. This is not to say that *every* patient with angina has completely exhausted his coronary reserve. In one patient (no. 9) in whom the pain occurred only with strenuous prolonged effort there was some capacity to dilate, but nevertheless below that seen in the normal. How often this will occur and what its relationship is to severity of the ischemic process is under investigation.

Failure of vasodilatation was also seen in 3 individuals who did not have clinical evidence of coronary insufficiency, but who showed a chronically increased left ventricular work load. This physiologic insufficiency without a clinical counterpart is similar to the pathologic findings that coronary vascular disease may be severe without the existence of coronary symptoms. Coronary symptoms without coronary disease, however, has rarely been demonstrated.[34]

Many patients appear with chest pain of uncertain etiology. Frequently, the history is atypical, the electrocardiogram negative, and the effect of standardized effort equivocal. The response of the coronary circulation to nitroglycerin while indicative only of physiologic coronary reserve insufficiency, may aid in objective evaluation of factors responsible for pain. At the very least, finding a fixed coronary resistance would indicate that the oxidative-nutritional reserve of the myocardium is in marginal balance. A measure of reactivity of the coronary circulation before and after a drug or surgical procedure designed to improve coronary blood flow could give invaluable objective information concerning its efficacy.

Action of Nitroglycerin. Basing their statements primarily on animal experimentation, numerous investigators have asserted that nitroglycerin is a coronary vasodilator.[35-37] This certainly appears to be true in normal and in mild cardiac subjects, but coronary dilatation was not seen in patients with coronary arterial disease or left ventricular overloading. Goodman and Gilman in fact suggested that "arteriosclerotic coronary arteries are not greatly affected by nitrite."[38]

Although myocardial efficiency fell in these abnormal groups, the decrease in calculated efficiency was related to a decreased work with a fixed myocardial oxygen consumption. Efficiency fell in the normal group also, but here the reverse was true—work was maintained as oxygen consumption increased.

Since oxygen extraction was maximal, increased supply was accomplished by increased coronary flow. These findings are consonant with the observation that nitroglycerin uncoupled oxidative phosphorylation.[39] When the amount of oxygen delivered to the tissue was restricted, the work output of the left ventricle of necessity decreased.

Nitroglycerin and Angina Pectoris. Fourteen of the 17 patients in this study had angina pectoris; in 9 of these 14, nitroglycerin was known to give relief of the ischemic pain. Yet as these observations would indicate, relief of pain is not easily explained by present theories regarding the action of nitroglycerin. The fact that coronary flow did not increase, but was fixed and occasionally decreased would show that relief was not due to *generalized* coronary vasodilatation. Myocardial oxygen utilization in relation to work done was actually greater after nitroglycerin, indicating that pain was not relieved by an improved myocardial efficiency. On the other hand, since none of the patients was studied during an actual anginal attack, one cannot be sure that an actual decrease in coronary flow may not have occurred due either to arteriolar constriction or vasospasm, and that the circulation was merely restored to normal by nitroglycerin. Finally, one observation seen throughout all these studies was that contractility of the heart diminished (possibly due to "uncoupling"). Cardiac output decreased, blood pressure decreased, and diastolic filling pressure of the ventricles decreased. One hundred years ago, Sir Lauder Brunton introduced the nitrites in the treatment of angina as a means of relieving the elevated blood pressure, which he believed caused the attack.[40] It may well be that there is a measure of truth in Brunton's premise. Nitroglycerin may achieve its remarkable clinical effects by decreasing the contractility of the heart rather than by relaxing the coronary vascular tree.

Summary

In 17 patients, 7 with coronary artery disease and 10 with increased left ventricular work load, observations of coronary, pulmonary, and systemic circulatory dynamics and myocardial gaseous metabolism were made before and after the sublingual administration of nitroglycerin. Fourteen of the 17 patients had angina pectoris.

Nitroglycerin resulted in a decrease in cardiac output, blood pressure, and left ventricular work in both "coronary" and "work" groups and caused a fall in systemic and pulmonary venous pressures.

Coronary blood flow and myocardial oxygen consumption were slightly increased at rest with a slightly decreased myocardial efficiency as compared to normal. Coronary vascular resistance was normal. Following nitroglycerin, coronary vascular resistance remained essentially fixed; coronary flow and oxygen consumption were unchanged or actually decreased; and efficiency fell.

These findings are believed related to prior exhaustion of the available vasodilator capacity of the heart, either by intrinsic coronary arterial obstruction or through hemodynamic overloading of the left ventricle by disease. The difference in reactivity between the normal and diseased coronary circulations is believed to afford an objective physiologic method of assessing the functional adequacy of the coronary circulation.

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Summario in Interlingua

In 17 patientes—7 con morbo de arteria coronari e 10 con augmento del carga de labor sinistro-ventricular—observationes relative al circulation coronari, pulmonar, e systemic e al metabolismo gasose myocardial esseva facite ante e post le administration sublingual de nitroglycerina. Dece-quatro del 17 patientes habeva angina de pectore.

Nitroglycerina resultava in un reduction del rendimento cardiac, del tension de sanguine, e del labor sinistro-ventricular in ambe gruppos e causava plus basse tensiones systemic e pulmono-venose.

Le fluxo de sanguine coronari e le consumption myocardial de oxygeno esseva levemente augmentate in stato de reposo, con leve re

fluctiones del efficacia myocardial in comparation con valores normal. Le resistentia del vasos coronari esseva normal. Post nitroglycerina, le resistentia del vasos coronari esseva essentialmente fixe. Le fluxo coronari e le consumption de oxygeno monstrava nulle alteration o, de facto, un reduction. Le efficacia declinava.

Es opinate que iste constatationes es relationate a un previe exhaustion del disponibile capacitate vasodilatatori del corde per (1) un intrinsec obstruction de arteria coronari o per (2) un supercarga hemodynamic del ventriculo sinistre in consequentia de morbiditate. Le differentia del reactivitate de normal e morbide circulationes coronari pare offerer un objective methodo physiologic pro evaluar le adequatia functional del circulation coronari.

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Moser, K. M., and Shea, J. G.: The Relationship between Pulmonary Infarction, Cor Pulmonale and the Sickle States. Am. J. Med. **22**: 561 (April), 1957.

Seven cases of sickle-cell anemia and sickle variants are presented in whom pulmonary infarction could not be explained on an embolic basis. It is suggested that as a consequence of the presence of large quantities of S hemoglobin these patients suffered pulmonary thrombosis in situ, leading to pulmonary infarction. The increased blood viscosity associated with sickling and the number of sickled cells predispose to stasis. The pathologic process may be potentiated by large quantities of S hemoglobin, low oxygen tension, poor pulmonary ventilation, fever, leukocytosis, exercise, and acidosis. All of these factors are present in such patients and are further aggravated by the circulatory consequences of anemia, especially congestive failure. Pulmonary infarction or "atypical pneumonitis" in the Negro should arouse suspicion and lead to a search for sickling. Cor pulmonale may be an ultimate consequence of multiple recurrent infarctions.

Kurland

Electrocardiographic Patterns in Man at High Altitudes

By ANDRÉS ROTTA, M.D., AND ANDRÉS LÓPEZ, M.D.

Electrocardiograms of healthy men both native and long-term residents at 14,900 feet above sea level have been obtained and classified according to their dominant pattern. Most of the tracings showed signs of either right ventricular hypertrophy or right bundle-branch block, incomplete and complete. Some of the mechanisms responsible for these electrocardiographic changes found at high altitudes, such as pulmonary hypertension, positional changes of the heart, and chronic hypoxia, are discussed.

THE effect of chronic hypoxia due to altitude on the right side of the heart is of particular interest. Measurements made on teleroentgenograms of the heart of normal subjects living permanently at an altitude of 14,900 feet have shown an increase in the transverse diameter of the heart and in the cardiac silhouette area, as well as a prominent pulmonary conus.[1-4] Complementary fluoroscopic studies have demonstrated that an increase in the volume of the right cavities rather than a total involvement is responsible for heart enlargement.[4, 5] More recently, by means of cardiac catheterization, a moderate but significant increase of the pulmonary artery pressure and of total pulmonary resistance has been found in men at high altitudes.[6] Finally, a variable grade of right ventricular hypertrophy has been found in a small number of postmortem observations on subjects at high altitudes dying from work accidents.[7]

The preceding information, as well as preliminary electrocardiographic observations carried out at this same altitude,[4] at lower altitudes,[8] and on miners without pulmonary silicosis from various altitudes and studied at sea level after several days of residence[9] suggests that normal men living at high altitudes must show some electrocardiographic signs of right ventricular hypertrophy. The work reported here was designed to shed some light on this problem. Accordingly, electrocardiograms of a group of normal subjects residing at high altitudes were taken and compared with normal standards at sea level.

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MATERIAL AND METHODS

One hundred and twenty electrocardiograms of healthy men, 20 to 54 years of age, and residents of Morococha (Peru), at 14,900 feet above sea level, were studied. Of the 120 tracings, 106 were of native Indians and 14 of white or mixed race born at sea level but having lived 15 to 30 years at high altitudes. Clinical examinations including x-rays and systemic arterial blood pressure were made in order to eliminate all possibility of respiratory or cardiovascular disorder. In some cases the arterial oxyhemoglobin per cent, blood volume, blood red cell count, and blood hemoglobin concentration were determined. In 7 cases with typical electrocardiographic patterns, right heart catheterization was performed following the method of Cournand and Ranges.[10] The results obtained by heart catheterization have been reported in detail in a previous publication.[6]

Electrocardiograms were taken during rest in the supine position, with Sanborn Viso-Cardiette and Cambridge Simple-Trol electrocardiographs. The standard leads, 3 augmented unipolar limb leads, and 7 unipolar precordial leads from RV_3 to V_6 were recorded. In 18 instances RV_3 was not registered; in 5 cases, the VE lead was recorded instead of RV_3, and in 6 additional cases leads from right precordium (RV_4, RV_5, and RV_6) were taken. In all tracings height and duration of the P, R, S, and T waves in standard and precordial leads were measured. The ventricular activation time (time of onset of the intrinsic deflection), from the beginning of QRS complex to the peak of R wave, was measured in V_1, V_5, and V_6. The mean electric axis of QRS and the R/S ratio in V_1, V_5, and V_6 were determined.

RESULTS

A preliminary study of the electrocardiograms permitted us to divide the tracings into 4 principal groups according to their dominant pattern: (a) right ventricular hypertrophy, (b) suggestive of right ventricular hypertrophy ($S_1S_2S_3$ pattern), (c) right

TABLE 1.—*Electrocardiographic Measurements in Twenty-Three Altitude Subjects with Pattern of Right Ventricular Hypertrophy*

Age (yrs.)	Heart rate/min.	Amplitude of P (mm.)	P-R interval (sec.)	QRS interval (sec.)	A' QRS	Ventricular activation time (sec.)		Amplitude of R (mm.)					Amplitude of S (mm.)				R/S ratio		
						V_1	V_6	VR	RV_3	V_1	V_5	V_6	RV_3	V_1	V_5	V_6	V_1	V_5	V_6
41	55	3.2	0.19	0.07	—172	0.039	0.022	6.5	8.9	9.3	9.7	6.2	2.5	3.7	7.4	6.5	2.51	1.31	0.90
26	58	1.5	0.18	0.08	—140	0.033	0.023	4.5	11.3	12.0	9.0	3.0	2.0	4.1	8.5	5.5	2.99	1.05	0.50
30	91	1.0	0.18	0.09	—115	0.035	0.030	8.0	7.0	9.0	4.5	2.0	3.1	3.0	9.5	8.0	3.00	0.47	0.25
40	60	3.3	0.18	0.09	—160	0.040	0.027	6.5	—	7.1	6.2	5.4	—	5.6	11.8	10.3	1.39	0.52	0.52
21	74	3.1	0.16	0.08	—170	0.035	0.032	6.9	9.0	9.2	9.1	5.8	0.3	2.7	6.0	6.8	3.40	1.13	0.85
32	62	2.4	0.17	0.08	—165	0.034	0.038	7.8	10.2	11.2	9.3	5.8	4.5	9.1	10.9	8.0	1.23	0.85	0.72
27	70	2.0	0.17	0.09	—135	0.031	0.039	7.9	9.8	10.8	9.0	6.2	3.8	8.5	9.1	7.0	1.27	0.98	0.88
39	55	3.1	0.19	0.09	—125	0.045	0.034	6.0	12.0	11.7	7.0	5.4	1.0	1.8	7.5	6.4	6.50	0.93	0.84
20	58	2.0	0.18	0.09	—110	0.040	0.043	6.5	6.8	7.0	5.4	5.0	4.3	5.1	8.5	7.2	1.37	0.63	0.69
25	75	1.0	0.16	0.08	—170	0.022	0.030	7.0	—	9.1	10.0	6.0	—	5.0	7.0	6.2	1.82	1.43	0.96
36	102	1.1	0.16	0.08	+170	0.035	0.030	4.9	12.0	11.0	6.2	4.0	1.5	3.2	11.0	7.0	3.45	0.56	0.57
39	65	2.5	0.19	0.09	+125	0.040	0.034	6.0	11.8	15.0	9.0	7.0	0.8	2.3	9.2	7.5	6.51	0.99	0.93
20	58	2.0	0.18	0.08	+110	0.032	0.040	6.5	9.0	7.0	10.0	9.0	4.0	3.5	11.0	9.0	2.00	0.90	1.00
25	65	2.5	0.17	0.10	+155	0.030	0.034	5.0	7.0	8.8	4.0	4.7	5.6	5.1	4.7	3.9	1.72	0.89	1.00
30	78	1.9	0.17	0.09	+126	0.022	0.035	5.3	7.8	7.3	5.0	3.0	3.7	6.2	7.9	6.6	1.17	0.63	0.45
36	82	1.8	0.18	0.09	+163	0.036	0.028	5.9	12.3	10.0	6.8	5.6	2.8	4.6	10.9	7.0	2.17	0.62	0.80
21	90	2.3	0.18	0.08	+152	0.039	0.031	6.8	13.2	11.2	7.7	6.5	3.7	4.9	11.7	8.0	2.28	0.65	0.81
30	64	2.4	0.17	0.10	+138	0.036	0.029	10.2	15.0	17.8	8.3	4.2	0.2	7.0	9.0	5.0	2.54	0.92	0.84
27	68	2.0	0.19	0.09	+167	0.037	0.032	4.3	7.5	8.5	7.5	5.0	4.2	6.0	8.0	6.0	1.41	0.93	0.83
20	78	1.8	0.19	0.08	+155	0.039	0.040	7.5	—	8.0	7.2	5.2	—	4.2	7.2	6.7	1.90	0.84	0.59
20	85	1.6	0.18	0.07	+122	0.035	0.036	7.1	15.4	16.8	5.2	2.6	2.0	3.2	6.0	5.3	5.25	0.86	0.99
44	58	1.1	0.18	0.08	+118	0.042	0.038	6.5	12.9	13.7	4.8	4.5	2.0	2.6	5.8	4.5	5.26	0.82	1.00
54	69	1.7	0.19	0.09	+150	0.043	0.040	6.3	7.2	7.0	6.3	5.2	4.2	6.0	12.2	10.0	1.16	0.51	0.52
Av. 34	70	2.0	0.18	0.08	—	0.035	0.033	6.5	10.3	10.3	7.2	5.1	2.8	4.7	8.7	6.9	2.7	0.84	0.75

bundle-branch block, incomplete and complete, and (d) normal.

A. Pattern of Right Ventricular Hypertrophy. In this group we have gathered all the tracings presenting a tall R wave, of 7 mm. or more, in RV_3, V_1, or both, with an R/S ratio greater than 1.0 in V_1 and less than 1.0 in V_5 or V_6.

Twenty-three electrocardiograms (19.2 per cent) showed a pattern that we have classified as right ventricular hypertrophy because they fulfilled several of the criteria followed by Sokolow and Lyon,[11] Myers et al.,[12] and others[13, 14] in the diagnosis of right heart enlargement. Nineteen of these 23 cases were native Indians and 4 were subjects from sea level with long-term residence in Morococha. In table 1 are outlined the principal measurements obtained from this group. The P wave was found to be within normal limits in almost all cases and slightly exceeded 3 mm. in height in only 4 instances. The P-R interval ranged from 0.16 to 0.19 second and the QRS between 0.07 and 0.10 second. The height of R in VR was 5 mm. or more in 20 instances and was between 4 and 5 mm. in the remaining 3 cases. QRS in V_1 or RV_3 had a qR pattern in 11 cases, Rs or RS in 7, and rsR in the remainder of the 5 cases; this last pattern could be considered as incomplete right bundle-branch block associated with right ventricular hypertrophy.[15] The electrical axis of QRS was found strongly deviated toward the right, between 110° and 170°, in 13 cases, and strongly deviated toward the left, between −110° and −172°, in 10 instances because these had the $S_1S_2S_3$ pattern in the standard leads. An increased depth of the S wave was found in the left precordial leads, and, as will be seen later, this is a frequent finding in the electrocardiogram of high altitudes regardless of the pattern of the tracing. The ventricular activation time ranged between 0.22 and 0.35 second in 11 cases, and between 0.35 and 0.45 second in the remaining 12. In 4 instances T was found inverted in leads II and III, and in 9 cases in lead III only. In precordial leads, T was found in-

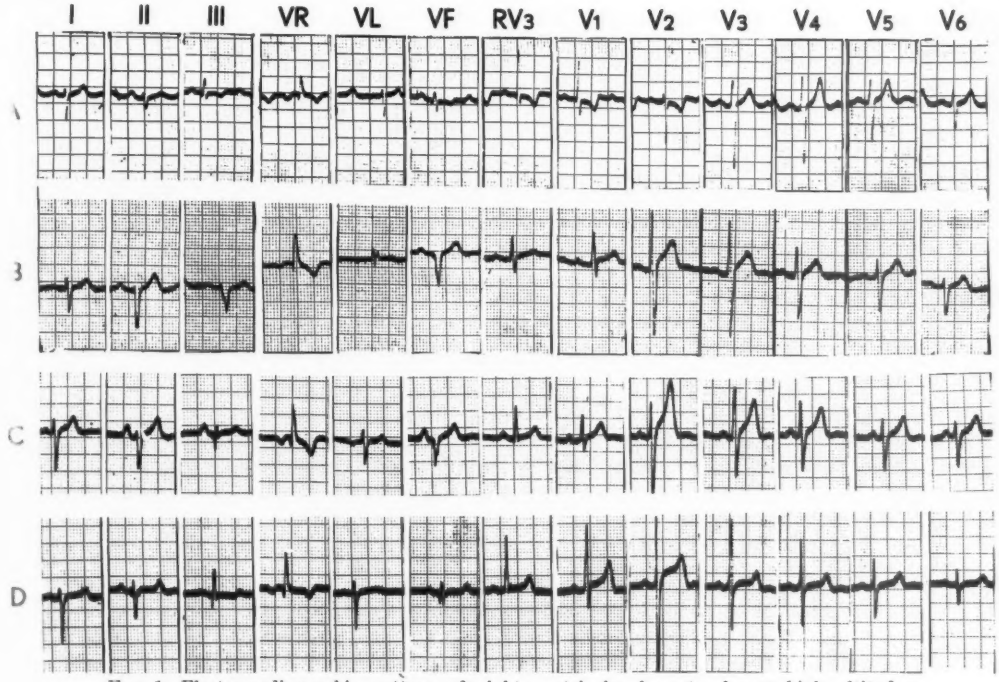

FIG. 1. Electrocardiographic pattern of right ventricular hypertrophy at high altitudes. Cases *A* and *B* were catheterized.

verted 11 times in V_1, 5 times in V_1 and V_2, and once in V_1, V_2, and V_3. The Q-T interval was normal in all electrocardiograms.

Four typical records of this group are reproduced in figure 1. Tracing *A* was in a 34-year-old man who had arterial oxyhemoglobin of 80.5 per cent, a hemoglobin concentration of 20.2 Gm./100 ml., a mean pulmonary artery pressure of 25 mm. Hg, a pulmonary vascular resistance of 415 dynes/sec./cm.$^{-5}$, and a cardiac index of 2.92 L./min./M.^{2} Tracing *B* was in a subject with 7[illegible].1 per cent of arterial oxyhemoglobin, and [illegible].5 Gm. per 100 ml. of hemoglobin; his mean pulmonary artery pressure was 28 mm. Hg; his pulmonary vascular resistance, 485 dynes/sec./cm.$^{-5}$; and his cardiac index, 2.97 L./min./M.^{2} The electrocardiographic pattern we have described in this group corresponds to the classic pattern of right ventricular hypertrophy found in congenital heart diseases as well as in chronic cor pulmonale. When in these pathologic processes, however, an attempt has been made to correlate the electrocardiographic pattern with pulmonary hypertension, pulmonary resistance or work of the right ventricle, a tall R wave in V_1 with R/S ratio greater than unity have been observed to occur in most cases only if the mean pulmonary artery pressure[16, 17] is more than 30 mm. Hg, the total pulmonary resistance[17, 18] is more than 750 dynes/sec./cm.$^{-5}$, or the work of the right ventricle[19, 20] is higher than 1 Kg./min./M.^{2} We did not obtain such high pressures or resistances in the 2 catheterized subjects. This observation suggests either that there must be other factors at high altitudes that contribute to the production of this type of electrocardiographic pattern or that the right ventricular hypertrophy may occur in the absence of marked increase of ventricular pressure, as has been found in cases of pulmonary stenosis.[21]

B. Electrocardiographic Pattern Suggestive of Right Ventricular Hypertrophy. In this group we have considered all records that

TABLE 2.—*Electrocardiographic Measurements in Thirty-Nine Altitude Subjects with $S_1S_2S_3$ Pattern*

Age (yrs.)	Heart rate/min.	Amplitude of P (mm.)	P-R interval (sec.)	QRS interval (sec.)	A' QRS	Ventricular activation time (sec.)		Amplitude of R (mm.)					Amplitude of S (mm.)				R/S ratio		
						V_1	V_6	VR	RV_3	V_1	V_5	V_6	RV_3	V_1	V_5	V_6	V_1	V_5	V
24	64	1.8	0.18	0.08	— 80	0.019	0.031	11.0	1.9	2.0	11.0	10.0	3.4	3.5	7.5	7.0	0.57	1.47	1.4
27	70	2.2	0.17	0.09	—110	0.017	0.030	7.0	2.9	2.7	15.0	12.0	1.7	2.9	8.5	8.0	0.92	1.67	1.5
40	60	2.4	0.19	0.09	—115	0.012	0.043	7.0	2.1	2.0	10.5	8.5	4.0	7.0	7.0	5.5	0.28	1.50	1.3
49	62	1.9	0.18	0.08	—112	0.028	0.029	6.0	3.5	4.0	9.0	3.4	2.5	4.8	15.0	8.0	0.85	0.60	0.4
50	58	2.3	0.18	0.08	—108	0.022	0.025	6.8	2.8	2.7	9.0	5.0	5.0	6.6	12.3	9.0	0.40	0.72	0.5
38	72	1.9	0.16	0.07	—118	0.016	0.022	5.0	1.8	3.0	5.2	3.5	3.8	7.5	5.0	3.5	0.40	1.04	1.4
28	76	2.0	0.16	0.08	—120	0.017	0.030	10.0	3.5	4.5	9.0	5.5	10.0	5.0	10.5	4.5	0.90	0.85	1.2
25	64	2.3	0.17	0.09	—110	0.031	0.032	10.5	5.9	4.5	8.2	5.0	8.5	12.8	15.5	13.0	0.35	0.52	0.6
35	69	2.4	0.18	0.09	— 85	0.018	0.024	6.5	—	1.0	11.0	9.5	—	9.0	7.5	6.5	0.11	1.46	1.7
53	62	2.0	0.17	0.08	— 95	0.023	0.028	7.0	—	1.5	10.8	6.0	—	6.6	13.6	6.8	0.22	0.79	0.9
25	56	2.4	0.18	0.08	—117	0.030	0.040	6.0	4.5	4.0	13.9	10.0	5.0	8.8	6.9	5.0	0.45	2.01	2.0
24	58	1.9	0.18	0.09	—118	0.039	0.032	7.5	2.4	3.3	7.6	7.5	5.0	7.0	9.0	8.5	0.47	0.84	0.8
40	75	2.2	0.16	0.08	—115	0.019	0.022	7.0	2.5	2.7	9.0	8.0	5.0	8.7	13.0	10.0	0.31	0.69	0.8
31	67	2.1	0.17	0.09	—112	0.034	0.038	10.7	5.8	4.6	8.2	5.0	7.7	12.5	15.2	12.9	0.29	0.53	0.3
40	65	2.0	0.17	0.09	—120	0.014	0.035	7.0	1.5	3.3	8.4	4.8	8.5	7.4	9.2	4.6	0.44	0.91	1.0
25	57	1.8	0.18	0.09	—117	0.030	0.040	6.0	4.0	4.0	13.9	10.0	5.0	8.8	6.9	5.0	0.45	2.01	2.0
22	62	2.2	0.18	0.08	—113	0.013	0.041	7.2	—	2.1	10.5	8.4	—	7.2	7.0	5.3	0.29	1.50	1.3
30	60	2.3	0.17	0.09	—122	0.016	0.038	7.4	3.0	3.2	8.3	4.8	5.3	7.3	9.0	4.7	0.43	0.92	1.0
21	80	1.1	0.13	0.08	—135	0.015	0.025	5.3	0.5	0.2	5.2	3.5	2.1	6.0	6.5	4.2	0.03	0.80	0.8
37	82	1.5	0.16	0.08	—115	0.015	0.030	6.5	0.5	1.6	12.0	6.5	1.0	8.5	9.5	5.0	0.18	1.20	1.3
23	98	1.2	0.19	0.07	—120	0.020	0.026	5.0	3.0	2.4	3.0	1.5	2.1	7.4	11.0	7.5	0.32	0.27	0.2
25	78	1.6	0.19	0.08	—110	0.025	0.030	7.1	3.7	4.5	7.0	2.7	10.0	10.8	15.5	11.0	0.41	0.45	0.2
28	79	1.2	0.13	0.08	—137	0.014	0.025	5.5	—	0.4	5.5	3.6	—	6.3	6.6	4.4	0.06	0.83	0.8
36	81	1.7	0.15	0.09	—112	0.016	0.029	6.8	—	1.6	12.3	6.8	—	8.5	9.8	5.0	0.18	1.25	1.3
22	96	1.5	0.19	0.08	—123	0.021	0.030	5.1	3.5	2.4	4.0	1.8	2.1	7.5	10.8	7.5	0.33	0.37	0.2
26	79	2.0	0.18	0.07	—111	0.026	0.030	7.2	—	4.0	7.5	2.8	—	10.2	15.1	11.4	0.39	0.49	0.2
28	72	2.3	0.17	0.09	—112	0.017	0.032	7.0	2.9	2.0	14.5	11.8	1.7	2.9	8.6	8.0	0.67	1.68	1.4
41	62	2.6	0.18	0.09	—160	0.039	0.027	6.0	5.3	5.6	6.2	5.5	4.5	5.8	12.8	11.0	0.96	0.48	0.5
20	79	2.4	0.18	0.08	—165	0.036	0.026	6.3	5.5	5.6	6.0	5.4	4.8	5.7	11.2	10.5	0.96	0.53	0.5
20	80	2.2	0.18	0.08	—168	0.038	0.029	6.0	5.5	5.9	6.3	5.2	4.5	6.2	12.2	11.2	0.95	0.51	0.5
21	99	1.2	0.19	0.08	—125	0.020	0.025	5.0	3.1	2.4	3.0	1.5	2.0	7.4	11.2	7.7	0.32	0.43	0.1
20	78	2.0	0.18	0.08	—122	0.031	0.040	6.9	4.5	4.3	13.7	9.8	5.1	8.6	6.5	5.0	0.50	2.10	1.9
43	79	2.3	0.17	0.09	—130	0.030	0.039	6.6	—	4.0	5.5	5.1	—	8.2	6.2	5.1	0.48	0.88	1.0
51	80	1.6	0.18	0.08	—170	0.039	0.031	7.2	5.9	6.8	7.2	5.8	5.0	6.8	11.9	11.0	1.00	0.60	0.5
49	67	1.5	0.19	0.07	—172	0.034	0.038	7.7	6.4	6.2	8.2	6.2	5.3	7.2	12.3	11.4	0.83	0.65	0.5
26	59	2.0	0.17	0.07	—115	0.035	0.039	6.1	3.9	4.0	12.8	10.0	5.0	8.5	6.5	5.0	0.57	1.96	2.0
21	80	1.4	0.14	0.08	—130	0.018	0.027	5.4	0.7	0.5	5.8	4.8	2.2	6.3	5.0	4.5	0.79	1.16	1.0
27	68	1.9	0.18	0.09	— 83	0.022	0.035	10.7	1.8	2.0	10.5	9.0	3.2	3.5	7.6	7.2	0.56	1.38	1.1
41	78	1.2	0.19	0.08	—108	0.025	0.032	7.2	3.9	4.8	7.8	6.2	10.0	10.9	7.2	6.9	0.44	1.03	1.0
Av. 32	72	1.9	—	0.08	—	0.024	0.031	7.0	3.3	3.2	8.8	6.2	4.7	7.4	9.3	7.3	0.44	0.95	0.9

presented main deflection downward directed in the standard leads with R less than 7 mm. in V_1 or RV_3 and R/S ratio less than 1.0 in V_1. Thirty-nine electrocardiograms (32.5 per cent) showed these features. Seven of them were of long-term residents and the remainder of native Indians. All these records (table 2) showed a notable left axis deviation, from −80° to −172°, an R more than 5 mm. in height in VR, and a deep S in the precordial leads. The height of P was normal in all instances. In 34 cases the ventricular activation time in V_1 ranged between 0.012 and 0.035 second, and between 0.035 and 0.039 second in the remaining 5 cases. The QRS complex showed a duration of 0.07 to 0.09 second. The R/S ratio was greater than 1.0 in RV_3 in 11 subjects; in V_5 or V_6 it was less than 1.0 in 23 instances, and greater than 1.0 in the other 16. Inversion of T was found in lead III in 12 cases, and in V_1 in 18 subjects; inversion of T in V_2 or V_3 was not found in any of the records of this group in contrast to that seen in the previous group.

Five tracings of this group are reproduced in figure 2. Cases *A* and *B* represent the 2 subjects who were catheterized. Tracing A was in a 20-year-old native Indian of More-

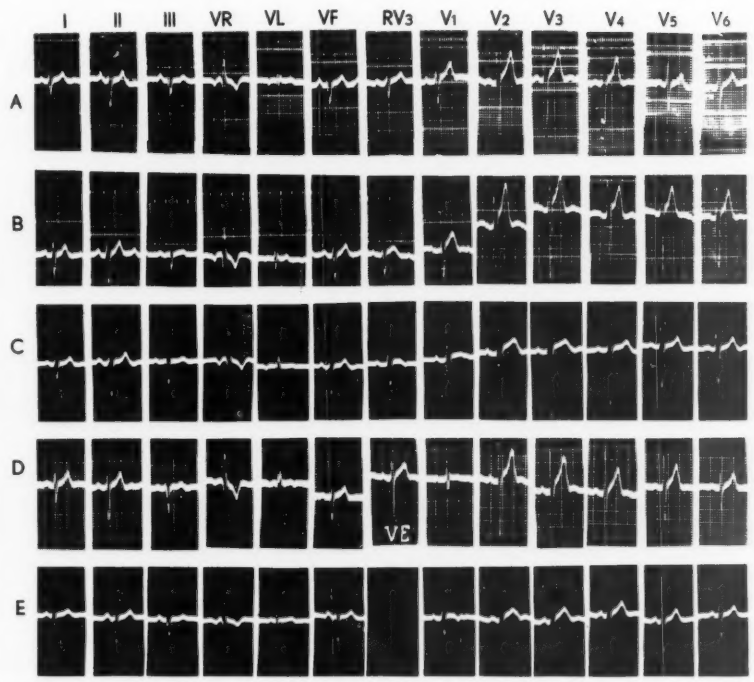

FIG. 2. Electrocardiograms with main deflection downward directed in the standard leads usually found at high altitudes. Cases *A* and *B* were catheterized.

cha whose arterial oxyhemoglobin was 81.3 per cent, and the blood hemoglobin 22.7 Gm./100 ml.; he showed a mean pulmonary artery pressure of 22 mm. Hg, a total pulmonary resistance of 292 dynes/sec./cm.$^{-5}$, and a cardiac index of 3.94 L./min./M.^{2} Tracing *B* was taken from a 27-year-old native Indian, in whom only the right ventricular pressure was obtained, with values of 29/3 mm. Hg for systolic and diastolic pressures.

Tracings with the main deflection directed downward in the standard leads have been rarely found at sea level, even in cases of cardiac or chronic pulmonary diseases.[22-30] This has been interpreted as normal variant, clockwise rotation of the heart on its long axis with the apex backward displaced, or as indicative of right ventricular hypertrophy, especially from the vectorcardiographic point of view.[30] This same pattern has been found more frequently in cases of chronic cor pulmonale, congenital heart diseases, cardiac infarction, and rheumatic involvement of the mitral valve.[36] In our study all these possibilities are excluded, since the tracings are of normal individuals. In 3 subjects who exhibited a typical $S_1S_2S_3$ pattern in the standard leads with R/S ratio less than 1.0 in V_1 and RV_3, additional leads from the right precordium were taken (RV_4, RV_5, and RV_6). In none of these cases did we find a tall R in such additional leads although the R/S ratio became greater than 1.0 in all the 3 cases. A tracing of this type is presented in figure 3, with additional leads of the right side. It can be observed that the R/S ratio was greater than 1 in RV_5.

With more severe criteria, most if not all of the tracings in this group should be considered as representative of right ventricular hypertrophy. We have separated them in a different group, however, because of the very special characteristics they present, as can be seen in figures 2 and 3, and table 2. It is

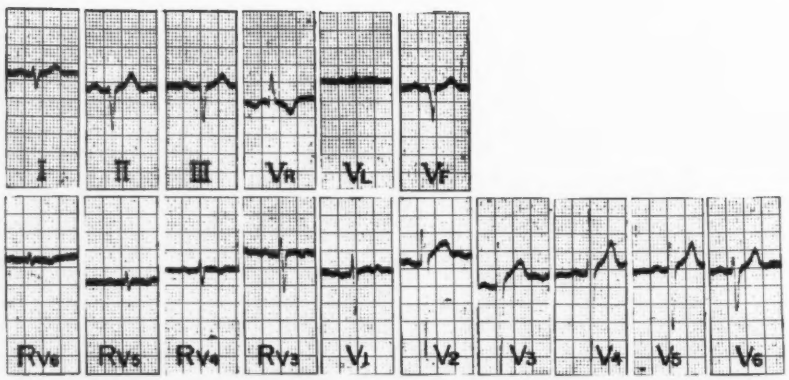

FIG. 3. Electrocardiogram with $S_1S_2S_3$ pattern at high altitudes in which additional precordial leads were taken. Observe that R/S ratio became higher than unit only in RV_5.

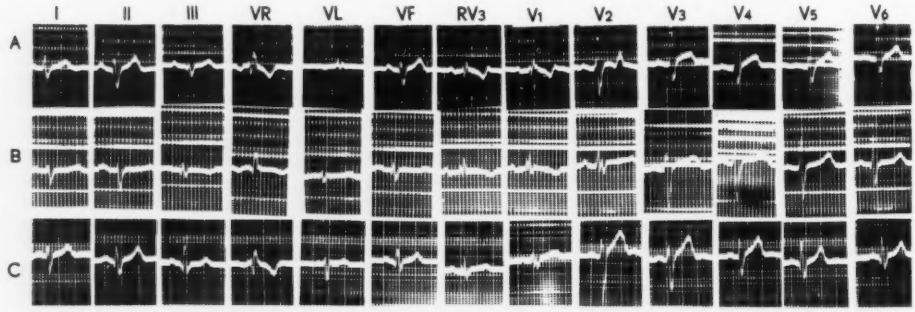

FIG. 4. Incomplete right bundle-branch block in man at high altitudes. Cases *A* and *B* were catheterized.

important that approximately 1 out of 3 normal subjects living at a high altitude shows an electrocardiographic pattern of this type.

C. Pattern of Right Bundle-Branch Block Incomplete and Complete. Thirty-seven cases (30.8 per cent) of our series showed a RSR′ pattern with a ventricular conduction time of more than 0.08 second. Following the criteria of Wilson and associates,[31] and of Barker and Valencia,[15] we have considered as incomplete right bundle-branch block the QRS interval ranging between 0.08 and 0.12 second, and as complete right bundle-branch block the QRS interval beyond 0.12 second. Of the 37 cases, 35 were classified as incomplete and 2 as complete right bundle-branch block. In none of the tracings was R higher than 10 mm. in V_1 or RV_3. In 16 instances QRS was W-shaped instead of M-shaped in right chest leads. In figure 4 are reproduced 3 electrocardiograms of this group. Tracings *A* and *B* were taken from 2 subjects who were catheterized. Tracing *A* was in a 22-year-old man whose arterial oxyhemoglobin was 79.4 per cent, and the blood hemoglobin content 19.2 Gm./100 ml.; the mean pulmonary artery pressure was 21 mm. Hg; the total pulmonary resistance, 294 dynes/sec./cm.$^{-5}$; and the cardiac index, 3.50 L./min./M.^{2} Tracing *B* was in a subject in whom only the right ventricular pressure could be obtained; it was 42/6 mm. Hg. Tracing *C* was from a white man residing for 28 years in Morococha. It is important that incomplete and complete right bundle-branch block have been associated with pulmonary hypertension and with right ventricular hypertrophy in congenital heart diseases[19, 32–34] as well as with chronic cor pulmonale.[14, 16, 17] It has been observed that the RSR′ pattern in right precordial leads is most

requently associated with low average systolic pressures, while a tall RV_1 pattern goes with high average systolic pressures.[35]

D. Normal Pattern. Twenty-one tracings 17.5 per cent) of all electrocardiograms obained did not present substantial modificaions in the configuration, amplitude, or direcion of the inflections as compared to the ormal standards established at sea level.[37, 38] Nine of the 21 cases, however, showed a modrate right axis deviation, between 90° and 02°, and a deep S wave in left precordial eads even though the R/S ratio was higher han 1.0 in V_5 and V_6. Likewise, a somewhat all R wave in VR was found in several cases although it did not reach 5 mm. in height. One subject of this group when catheterized had a right ventricular pressure of 32/4 mm. Hg.

Discussion

It is evident that the first 3 electrocardiographic patterns we have found in normal subjects living permanently at high altitudes are similar to cases of congenital heart diseases or chronic cor pulmonale associated with right ventricular hypertrophy found at sea level. Normal tracings should cause no surprise, since normal electrocardiograms have been found at sea level in cases of proved right ventricular hypertrophy.[19, 39, 40] The mechanism for the production of right ventricular hypertrophy at high altitudes appears to be the increased pulmonary pressure that has been found at this altitude.[6] However, as we have already mentioned, the electrocardiographic signs of right ventricular hypertrophy or right bundle-branch block in congenital heart diseases and in chronic cor pulmonale rarely appear at the levels of pressure resistance that we have found in our catheterized cases. This suggests that the electrocardiogram at high altitudes is very expressive in detecting right ventricular hypertrophy and leads us to discuss some aspects of the problem.

First we shall dwell on the possible role that the positional changes of the heart plays in the pathogenesis and prevalence of the negative deflections of QRS complex in the standard and precordial leads. The changes in the position of the heart at high altitudes may be conditioned (a) by the broadening of the thorax with an elevation in the diaphragm, (b) by increased minute ventilation, higher vital capacity, and increased residual air,[41] and (c) by an increased amount of pulmonary blood volume.[42] All these mechanisms of respiratory adaptation may contribute in determining a clockwise rotation of the heart on its long axis and backward displacement of the apex. These changes in turn would be responsible for the predominantly downwardly directed QRS complexes in all 3 standard leads, giving rise to one of the most important characteristics of the electrocardiogram at high altitudes.

Another possibility to consider in the interpretation of the exaggerated changes in the electrocardiogram at high altitudes might be the existence of a slight degree of left ventricular hypoplasia which would enhance the electrocardiographic signs of the right side. We have no direct data based on autopsy material to settle this point, but it has been proved that at high altitudes the cardiac output is normal while the systemic arterial pressure is low, as compared to that found at sea level,[4, 43] with a resultant diminution of work for the left ventricle at high altitudes.

A third possibility to consider is the permanent exposure to anoxic environment throughout all or most of life. Apparently this would be an important factor in the development of the right ventricular hypertrophy at high altitude, since it has been demonstrated that electrocardiographic patterns of subjects from sea level taken to high altitude and left there for up to 1 year do not show the characteristics seen in those of native Indians or long-term residents.[44]

The role of anoxia itself as a primary mechanism in the pathogenesis of the electrocardiographic patterns cannot be seriously considered, since anoxia acting as a general mechanism could produce biventricular hypertrophy of the heart with the concomitant electrocardiographic changes.

Finally, since the different patterns described in this study have been found in na-

tive Indians as well as in non-Indians living for a long time at high altitudes, we exclude race as well as any special process of natural acclimatization of subjects born at high altitudes as factors in the production of electrocardiographic changes.

Summary

Of 120 electrocardiograms of healthy adult subjects, natives or long-term residents of Morococha, Peru (14,900 feet above sea level), 23 (19.2 per cent) presented definite characteristic signs of right ventricular hypertrophy, 39 (32.5 per cent) showed highly suggestive signs of right ventricular hypertrophy, 37 (30.8 per cent) were classified as right bundle-branch block (2 cases as complete and 35 as incomplete), and 21 (17.5 per cent) were within normal limits.

In most of the electrocardiograms a predominance of negative deflections in the QRS complex was observed in the standard as well as in the precordial leads regardless of the dominant pattern. This finding gives the electrocardiogram at high altitude a special characteristic that is not usually seen at sea level. The mechanisms involved in this phenomenon are discussed with special reference to the positional changes of the heart.

The electrocardiogram confirms the anatomic and radiographic findings of right ventricular hypertrophy previously obtained in normal individuals at high altitude. It is believed that the right ventricular hypertrophy is related to the pulmonary hypertension that is usually found in man at high altitudes.

Summario in Interlingua

Inter 120 electrocardiogrammas ab normal adultos, nativos o residentes permanente de Morococha in Peru (4.500 m supra le nivello del mar), 23 (o 19,2 pro cento) presentava definitemente signos characteristic de hypertrophia dextero-ventricular, 39 (o 32,5 pro cento) monstrava signos multo suspecte de hypertrophia dextero-ventricular, 37 (o 30,8 pro cento) esseva classificate como casos de bloco de branca dextere (2 complete e 35 incomplete), e 21 (o 17,5 pro cento) esseva intra le limites del norma.

In le majoritate del electrocardiogrammas un predominantia de deflexiones negative in le complexo QRS esseva observate in le derivationes standard e etiam in le derivationes precordial, sin reguardo al typo predominante de configuration. Iste constatation attribue a electrocardiogramma de grande altitudes un characteristica special que non es incontrate usualmente al nivello del mar. Le mechanismos responsa bile pro iste phenomeno es discutite, con referentias special al alteration del position del corde.

Le electrocardiogramma confirma le constatation anatomic e radiographic de hypertrophia dextero-ventricular previemente reportate pro individuos normal a grande altitudes. Es opinate que iste hypertrophia dextero-ventricular es relationate al hypertension pulmonar que es usualmente observate in homines a grande altitudes.

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Witham, A. C., and Ellison, R. G.: Diagnosis of Ostium Primum Defects of the Atrial Septum. Am. J. Med. **22**: 593 (April), 1957.

Five patients with ostium primum defects are presented in order to outline a distinctive clinical syndrome that should allow preoperative diagnosis. Unlike ostium secundum defects, patients with ostium primum defects frequently have difficulty in childhood. Prominence of the left chest is a manifestation of the early enlargement of the heart. Cyanosis and clubbing are occasionally present. The parasternal systolic murmurs are variable and may be absent. Ostium primum defect may be suspected if the murmur is loud, associated with a thrill, and located higher than the usual murmur of interventricular septal defect. A separate systolic murmur at the apex, recorded in all these patients, is 1 of the auscultation features by which this defect is suspected. Also significant is an apical first sound less intense than the second. Left ventricular hypertrophy may be present. The electrocardiogram usually reveals incomplete right bundle-branch block but may show right ventricular hypertrophy. The P-R interval is prolonged. Fluoroscopy reveals right and left ventricular hypertrophy and increased pulmonary flow. Catheterization demonstrates a large left-to-right shunt. The majority of the criteria for separation from the more common atrial septal defects depends on the presence of either a cleft mitral leaflet or an incompetent common atrioventricular valve.

Kurland

Water and Salt Excretion after Intravenous Salt Load in Hypertensive Subjects

By T. D. Ullmann, M.D., S. H. Blondheim, M.D., S. Dikstein, M.Sc., Ph.D., and D. Ben-Ishay, M.D.

Intravenous salt-loading tests were performed in 20 hypertensive and 31 normotensive subjects. During the following 5 half-hour collection periods both water and salt excretion by the hypertensive subjects was higher than by the normotensive ones. The diuretic response was much more prolonged and more pronounced than the saluretic response and appears to be a primary response to the salt load, characteristic of the hypertensive state. The increased salt excretion is in part to be explained as the consequence of the increased water excretion. At moderate flow rates a salt-retaining mechanism could be demonstrated which is obscured at the higher rates of urinary flow that usually follow the salt load.

AN ABNORMALITY in the renal excretion of salt in the hypertensive state has been assumed for many years. It has been claimed by some authors that salt retention is a basic physiologic disturbance of the hypertensive state.[1, 2] On the other hand, more recent reports indicate that hypertensive patients in the early stages of their disease and animals with experimental hypertension tend to excrete salt during acute experiments more rapidly than do normal subjects.[3–15]

Most of these experiments have been carried out under conditions of increased urinary flow after oral or intravenous administration of large amounts of fluid, intravenous administration of hypertonic salt solutions, or osmotic diuresis caused by mannitol given intravenously. Since the rate of urinary flow may influence the rate of excretion of solutes,[16–20] it appeared to us that the excretion of salt in the hypertensive as compared with the normal state could be evaluated only in terms of the simultaneous excretion of water. In the following study the differences in the excretion of both water and salt after intravenous load of hypertonic saline between normal subjects and patients with hypertension are analyzed.

Material and Methods

The subjects were 20 hypertensive patients in the early stages of their disease and without complications, as judged from their histories and physical status. The control group comprised 31 patients without hypertension, cardiovascular, renal, or hepatic disease. The subjects in both groups had normal urinary findings, normal urinary concentrating power, and creatinine clearances within the normal range. The subjects in both groups were not restricted in their intake of salt during the days preceding the tests.

Salt-loading tests were performed in the morning after a very light breakfast. After urine collection for 30 minutes through an indwelling catheter, 5 Gm. of sodium chloride per square meter of body surface were given intravenously as a 5 per cent solution over a period of 30 minutes. The urine was collected during this period and for 5 more consecutive periods of 30 minutes each. The patients were allowed to drink up to 200 ml. of water if they desired. Blood and urine samples were obtained before the intravenous salt solution was given, and at the end of the last collection period, for the determination of sodium chloride and creatinine. The urinary volume and the excretion of sodium and chloride during the 5 periods following the end of the intravenous infusion were compared in the 2 groups.

Results

The urinary flow was significantly higher in the hypertensive group than in the normal during each 30-minute collection period after

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TABLE 1.—*Urinary Responses after Intravenous Sodium Chloride Load*

		Half-hour collection periods 1	2	3	4	5
Urinary volume (ml./min./M.² body surface area)						
Normal subjects	Mean	0.76	0.86	0.91	0.89	0.89
	S.D.	0.29	0.33	0.39	0.47	0.46
	n	31	31	30	30	25
Hypertensive subjects	Mean	1.72	1.75	1.67	1.51	1.53
	S.D.	1.26	1.27	0.92	0.83	0.92
	n	20	20	20	20	17
	t	4.09	3.76	4.0	3.35	2.95
	p	<0.001	<0.001	<0.001	0.001	<0.01
Sodium excretion (mEq./min./M.² body surface area)						
Normal subjects	Mean	0.186	0.209	0.219	0.220	0.211
	S.D.	0.092	0.073	0.097	0.084	0.087
	n	31	31	30	30	25
Hypertensive subjects	Mean	0.302	0.286	0.286	0.242	0.240
	S.D.	0.228	0.198	0.151	0.128	0.135
	n	20	20	20	20	17
	t	2.53	1.99	2.2	1.31	0.85
	p	<0.02	0.05	<0.05	0.2	<0.4
Chloride excretion (mEq./min./M.² body surface area)						
Normal subjects	Mean	0.187	0.204	0.213	0.189	0.201
	S.D.	0.084	0.071	0.074	0.084	0.082
	n	31	31	30	30	25
Hypertensive subjects	Mean	0.285	0.270	0.260	0.223	0.223
	S.D.	0.183	0.160	0.122	0.110	0.120
	n	20	20	20	20	17
	t	2.64	1.99	1.7	0.92	0.7
	p	<0.02	0.05	<0.4	<0.1	<0.5

administration of hypertonic saline. The excretion of sodium and chloride was also higher in the hypertensive group than in the normal subjects. However, this difference was less pronounced than the difference in water excretion, and was significant only during the first 2 collection periods after infusion (table 1).

In order to find out if the excretion of salt is related to the rate of urinary flow in the same way in both groups of subjects, the excretion of sodium and of chloride was plotted against the corresponding urinary flow. Separate analyses were made for the hypertensive and the normotensive subjects. Only the 2 periods immediately following the end of the sodium chloride infusion were chosen because the effect of secondary compensatory mechanisms might subsequently obscure the relationships (figs. 1 and 2).

For the plotting a method was chosen that is based on the work of Dole:[21] if logarithm of the relative clearance of any substance ($\log \frac{\text{clearance } x}{\text{clearance inulin}}$) is plotted against the reciprocal rate of urinary flow ($1/v$), an approximately straight or slightly curved line results, the slope of which is a measure of its tubular reabsorption.

When our data were plotted in this manner,* a definite positive relationship became evident between the urinary flow and the clearance of sodium and chloride in both

*The absolute clearances of sodium and chloride were plotted instead of their relative clearance because inulin clearances were not performed. However, since in most instances creatinine clearances were calculated and found to be unchanged during the first 2 periods after infusion as compared with a control period before infusion, and since the serum concentrations of sodium and chloride were found essentially unchanged throughout the experiment, it can be assumed that the substitution of absolute clearance figures for relative clearances did not entail a significant or systematic error.

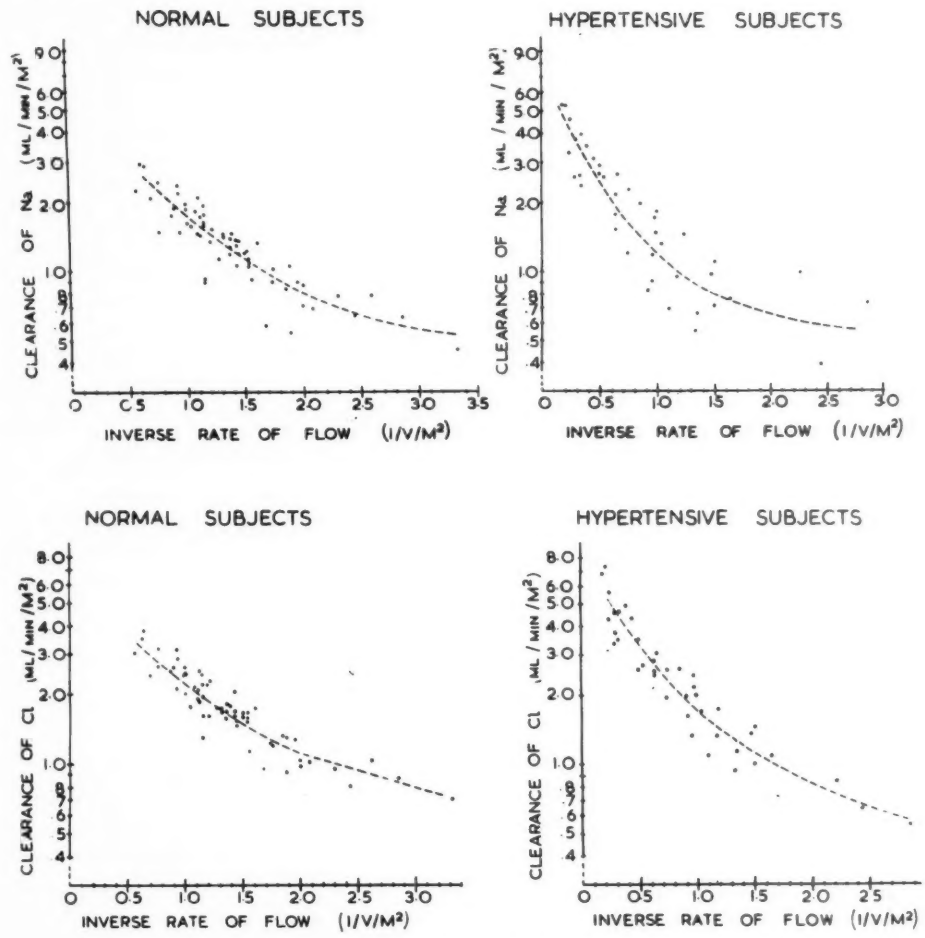

FIG. 1 *Top.* Clearance of sodium (C_{Na}) in ml./min./M.² (*ordinate*) as function of flow in ml./min./M.² (*abscissa*).

FIG. 2 *Bottom.* Clearance of chloride (C_{Cl}) in ml./min./M.² (*ordinate*) as function of flow in ml./min./M.² (*abscissa*).

roups (figs. 1 and 2). High urinary flow tes were associated with high excretion of dium and chloride; with decreasing urinary w the amounts of sodium and of chloride caping tubular reabsorption and appearing the urine became progressively smaller. The plots for the normotensive and hyper- nsive subjects showed marked differences various aspects, as seen from the curves ted (by inspection) through the plotted ints. Regression lines were calculated from our data, on the assumption that the curves may be represented with reasonable accuracy by straight lines, and the differences in the slopes of the regression lines for the hypertensive and the normotensive subjects were found to be statistically significant: $t_{Na} = 4.0$; $t_{Cl} = 4.85$.

Furthermore, the curves, when superimposed, crossed each other at points corresponding to flow rates of about 2 ml. per minute ($1/r = 0.5$). At higher rates of flow the

sodium and chloride clearances in the hypertensive subjects were higher than in the normotensive ones; at medium and low flow rates the hypertensive subjects excreted less salt than did the normotensive subjects.

Discussion

The data presented show that hypertensive subjects react to intravenous administration of hypertonic salt solution with a greater output of water, as well as of salt, than do normal subjects. In similar experiments other workers also found increases both in water and in salt excretion by hypertensive subjects. However, the possible relationship between the increased diuresis and saluresis has not been clearly formulated.[5, 7, 8, 15] Most workers seem to assume that the increased rejection of salt by the renal tubules is the cause of the increased rejection of water. This assumption does not seem to be valid, however, for those experiments in which higher flow rates were obtained in hypertensive than in normotensive subjects by the administration of isotonic or solute-free fluids.[3, 9, 10] The increased diuretic response in these experiments cannot possibly be the result of increased solute excretion, but must be regarded as a primary reaction of the hypertensive subjects to the experimental procedure.

On the other hand, the increased excretion of salt in all the reported experiments can be explained, at least in part, as the consequence of the high rates of urinary flow. The existence of such a relationship between urinary flow and salt excretion is apparent from the figures correlating the data of our experiments. A similar interpretation has been given by various workers to the increased sodium and chloride excretion observed during osmotic and water diuresis in man and in animals.[16–19] Moreover, a positive correlation between urinary flow and solute excretion has also been found for substances which were present only in small amounts in the glomerular filtrate, and which therefore could not in themselves constitute a solute load causing osmotic diuresis.[20] It has been suggested that the increased diuresis sweeps salt out of the proximal tubule faster than the distal tubule can handle it.[22]

It seems reasonable therefore to assume that the renal response of hypertensive subjects to the various experimental stimuli is primarily one of increased urinary output and that the increase in salt excretion is, at least in part, the consequence of the increased rate of urinary flow. Moreover, it is possible that the more rapid excretion of salt is an additional, separate expression of the same regulatory mechanism that causes the increased diuretic response in hypertensive subjects. The basic physiologic mechanism causing increased diuresis and—directly or indirectly—increased saluresis may be a reaction to the overexpansion of the extracellular fluid space. This mechanism, then, appears to be brought into action more readily in the hypertensive than in the normotensive state.

In contrast to the increased salt excretion under conditions causing high rates of urinary flow, our figures show that at moderate or low flow rates—below 2 ml. per minute—the hypertensive subjects excreted *less* salt than did the normotensive subjects at *the same* rates of flow. This phenomenon indicates a more complete tubular reabsorption of salt in the hypertensive subjects and may be a manifestation of the postulated salt retaining mechanism in the hypertensive state. As can be seen from our data, this mechanism is apparent only at low or moderate flow rates; under experimental conditions leading to high rates of urinary flow, it is abolished or obscured by the increased saluresis accompanying the increased diuresis.

A comprehensive description of the behavior of hypertensive subjects, as compared with normotensive ones, would therefore have to include their increased diuretic and saluretic response to salt and fluid loads, as well as a relative salt retention. The increased diuresis appears to be a more constant and a more pronounced feature than the increased salt excretion. The relative salt retention becomes manifest only at urinary flow rates up to about 2 ml. per minute and becom-

bscured under conditions causing higher ates of urinary flow.

Summary

In acute salt-loading experiments, hypertensive subjects excreted both water and salt t significantly higher rates than normal subects. The difference in the diuretic response vas greater and more pronounced than the lifference in the saluretic response.

This increased salt excretion by hypertensive subjects may be explained in part as he consequence of the increased rate of water xcretion, and in part as the direct effect of regulatory mechanism, which causes both liuresis and saluresis and which is more active in the hypertensive state.

Although the hypertensive subjects as a group excreted salt more rapidly than did the normotensive ones, at lower rates of urinary flow, up to about 2 ml. per minute, the salt excretion by the hypertensive subjects was less than by the normotensive ones. This observation is interpreted as the manifestation of a "salt-retaining mechanism" in the hypertensive state, which becomes obscured under conditions causing increased diuresis.

Acknowledgment

The valuable technical assistance of Mrs. L. Ullmann is gratefully acknowledged.

Summario in Interlingua

In experimentos a cargation acute con sal, subjectos hypertensive excerneva aqua e sal on significativemente plus alte intensitates que subjectos normal. Le differentia inter le esponsas diuretic esseva plus grande e plus ronunciate que le differentia inter le reponsas saluretic.

Le augmentate excretion de sal in subjectos ypertensive pote esser explicate in parte mo le consequentia del intensificate excreon de aqua e in parte como le effecto directe un mechanismo regulatori que initia le direse e le salurese e que es plus active in le ato de hypertension.

Ben que le subjectos hypertensive, considere como un gruppo, excerneva sal plus pidemente que le subjectos normotensive, in caso de plus lente fluxos de urina, i.e. usque a un volumine de circa 2 ml per minuta, le excretion de sal per le subjectos hypertensive esseva inferior a illo de subjectos normotensive. Iste observation es interpretate como le manifestation de un "mechanismo de retention de sal" in le stato de hypertension. Iste manifestation es obscurate sub conditiones que causa un augmento del diurese.

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Duguid, J. B., and Robertson, W. B.: Mechanical Factors in Atherosclerosis. Lancet **1**: 1205 (June 15), 1957.

The author reviews the evidence for the complementary roles of thrombogenic and mechanical factors in atherosclerosis. The mechanical hypothesis is that impairment of the elasticity or flexibility of an artery must lead to the structural disorganization that is seen in atherosclerosis. Atheroma results from the tearing and destruction of tissues resulting from the thickening and loss of elasticity of the intima. Arterial narrowing results from mural thrombosis formation followed by endothelial proliferation and incorporation in the wall becoming a fibrous thickening of the intima. One result is a loss of elasticity and flexibility and, in the case of large areas, dilatation of the vessel. Intimal hemorrhage, frequently found when carefully sought, provides support for the mechanical hypothesis, since it indicates that the forces disrupting the intima are active in living tissues. Many of the fatty changes of atherosclerosis according to this hypothesis are the products of hemorrhages or thrombi. But intimal damage also results in reduced tissue pressure at the points of loosening with resultant drawing of lipid-rich body fluids into these spaces. The genesis of atherosclerosis is thus traced from initial damage to the vessel wall, thrombosis, intimal thickening, and further vascular disruption. The dangers of atherosclerosis result from loss of control of the factors in blood or tissue that regulate thrombosis.

KURLAND

Spinal Epidural Hematoma during Anticoagulant Therapy

By Bertram M. Winer, M.D., Simon Horenstein, M.D., and Albert M. Starr, M.D.

Spinal epidural hematoma complicated the course of anticoagulant therapy of cerebrovascular disease in a patient in whom observations of multiple aspects of coagulation had been obtained. Examination of this case and a review of the literature allow delineation of a syndrome that should aid in early diagnosis of spinal epidural hematoma. It is clear that coumarin derivatives induce multiple coagulation defects, which vary quantitatively and qualitatively with time. Contemporary evaluation of the benefits and risks of long-term anticoagulants is beset by many problems that have not been fully resolved.

SPINAL epidural hematoma in the absence of trauma or malformation of spinal vessels is an exceedingly rare disorder. However, in recent years, at least 3, and possibly 4, instances have been reported as complications of anticoagulant therapy.[1-4]

The purposes of this paper are 4-fold: (1) to report an additional occurrence of spinal epidural hematoma in a patient on long-term anticoagulant therapy for cerebral vascular disease; (2) to delineate a syndrome that should aid in the prompt recognition of spinal epidural hematoma when it is still amenable to therapy; (3) to consider the coagulation defects induced by a coumarin derivative; and (4) to discuss the problem of evaluation of the benefits and risks of anticoagulants in cerebral vascular disease.

Case Report

A 70-year-old woman was admitted to the Beth Israel Hospital in May 1954 because of the sudden onset of nausea, vomiting, and vertigo. A right lateral medullary tegmental syndrome evolved, as evidenced by crossed dissociated hypalgesia involving the right face and the left side of the body, rhythmic ataxia of the right upper extremity, and right Horner's syndrome. The vertigo gradually subsided but the other neurologic abnormalities persisted. Additional findings included mild diabetes mellitus and labile hypertension.

In September 1956, the patient experienced a transient episode of confusion, slurred speech, right facial weakness, and urinary incontinence. In the following week she developed lethargy, anorexia, defective memory, and blurred vision. Physical examination revealed the neurologic residuals of the previous illness but no new abnormalities. The cerebral spinal fluid was normal. An electroencephalogram was diffusely abnormal. Routine hemogram, urinalysis, blood nonprotein nitrogen, and 1-hour postprandial blood sugar were normal. Chest roentgenogram revealed a large left pulmonary artery; the left ventricle and thoracic aorta were dilated.

Three weeks later nausea, irritability, and visual hallucinosis appeared. Neurologic examination at this time disclosed a relative left superior quadrantanopia. The tendon reflexes had become increased on the right and a left extensor plantar response was present. Over the next week she recovered from her confusion, ophthalmic palsy, and visual field defect.

Dicumarol was thereupon administered by mouth (fig. 1). A rapid fall in prothrombic activity was obtained as measured by a modified Quick 1-stage prothrombin method.[5] Beginning with the third week determinations* of proconvertin activity[6] and prothrombin (Owren method)[7] were obtained at intervals of 1 to 2 weeks for the following 7 months. In the last 6 months of this period prothrombic activity by the Quick 1-stage method ranged from 8 to 15 per cent of normal (20 to 30 seconds). Proconvertin was reduced to approximately the same percentage levels and correlated well with the prothrombic activity found by the Quick method. However, the prothrombin levels were for months much less depressed, but gradually fell to the 10 per cent level. In the last 4 months of therapy only a Quick prothrombin time was obtained and this was done in a different laboratory. The patient received 25 mg. of Dicumarol daily during the last 8 months of ther-

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*Kindly performed by Miss Angelina DiFrancesco, technician in the laboratory of Dr. Benjamin Alexander, Beth Israel Hospital.

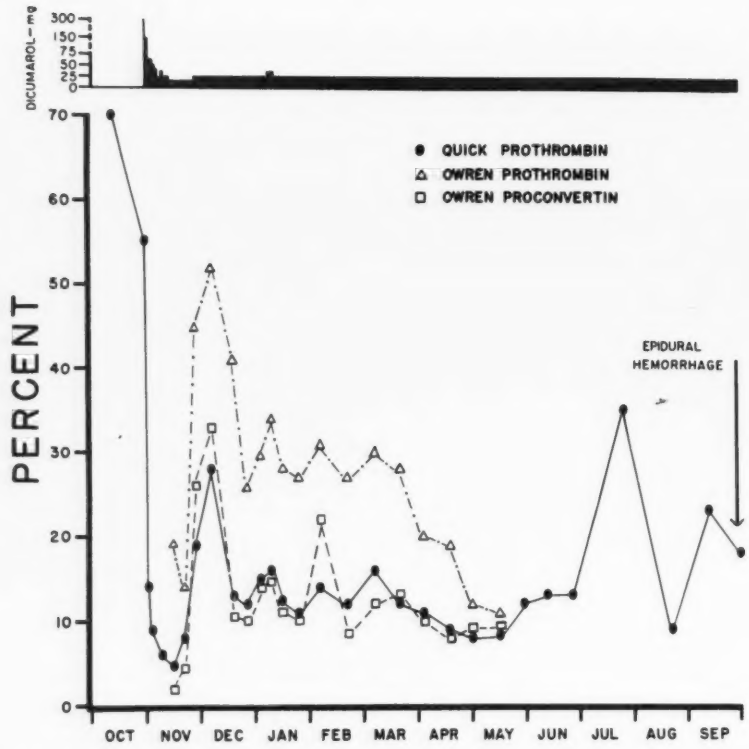

FIG. 1. The effect of Dicumarol on the Quick prothrombic activity, proconvertin, and prothrombin itself.

apy. Her clinical state remained stable through this interval.

On September 28, 1957, she arose to void and defecate. While returning to bed she experienced sudden severe pain between her shoulder blades. Six hours later she was unable to move her legs and was incontinent of urine. Thirty hours after the onset of the pain she was readmitted to the hospital. Examination now revealed drowsiness, moderate ataxia of the right upper extremity, and a right Horner's syndrome, but no other neurologic abnormality above the costal margin. The thoracic spine was tender between the sixth and eleventh vertebrae, maximally at the eighth. There was flaccid paralysis of both lower extremities. The tendon reflexes were absent. The plantar reflexes were bilaterally extensor with a crossed extensor response. Position sense was lost in both lower extremities below the hip. Vibration sense was absent below the iliac crest. Pinprick sensation was completely lost below the inguinal ligament bilaterally including the lower sacral segment. There was a shading loss of pinprick below the costal margin on each side. Thermal sensation and touch were similarly affected.

Lumbar puncture between the fourth and fifth interspaces revealed clear, acellular, yellow-brown fluid with a pressure of 35 mm. of cerebrospinal fluid. Intentionally, only a few drops of cerebral spinal fluid were collected. There was a complete dynamic block both to manual compression of the jugular veins and to jugular compression by means of a blood pressure cuff inflated to 40 mm. Hg. There was prompt response upon abdominal compression. One milliliter of pantopaque was then introduced into the subarachnoid space. The myelogram demonstrated a complete block between thoracic vertebrae 11 and 12 (figs. 2 and 3). At this time prothrombic activity was 18 per cent of normal, as measured by the Quick 1-stage prothrombin method.

Fifty milligrams of vitamin K_1 were administered intravenously. Three hours later, 45 hours after the onset of symptoms, a laminectomy was performed between the seventh and twelfth thoracic vertebrae under local anesthesia with n

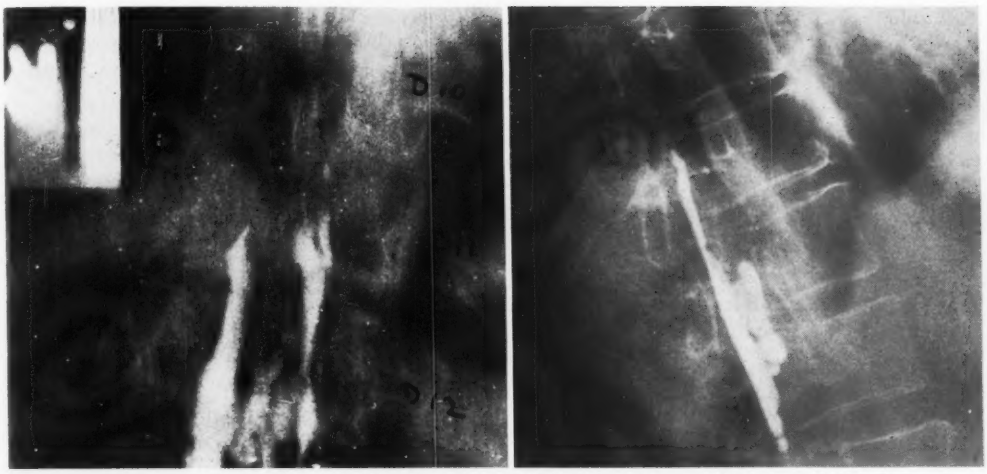

FIG. 2 *Left.* Anteroposterior view with the patient in head-down position. Myelographic demonstration of complete spinal block.

FIG. 3 *Right.* Lateral view with the patient in head-down position. Myelographic block and widening of the dorsal epidural space at T_{12} are evident.

unusual bleeding. The ligamentum flavum was bluish in color. Upon incision a blood clot extending from the sixth to eleventh thoracic spines was found in the dorsal epidural space. It was not adherent to the dura. The original site of bleeding was not identified. The spinal cord pulsated upon removal of the hematoma. The dura mater was not opened.

Postoperatively there was no recovery of the neurologic defects. Cerebral spinal fluid dynamics were normal 1 week after the operation. Brownish pigmentation was still evident in the spinal fluid. In the ensuing 6 months, there was return of pain sensation in the right lower extremity, but no other improvement in function. The paraplegia has persisted.

DISCUSSION

The evolution of spinal epidural hematoma as observed in our patient and in those reviewed[1-4, 8-12] presents a pattern that can be recognized with ease. Acute back pain, rapidly progressive spinal cord and nerve root deficit, usually with complete spinal block, accompanied by a brownish pigment in acellular cerebrospinal fluid are characteristic. Critical determinants are the location of the bleeding point, the volume of the vertebral canal relative to that of the spinal cord in the affected area, the proximity of intervertebral foramina, the presence of coagulation defects, and the final volume of the hematoma. These factors determine the degree of embarrassment of spinal cord circulation as well as the amount of pressure necrosis. The long vertical extent of the lesion, particularly if located in the lumbar or cervical enlargement of spinal cord, may in addition produce severe atonic flaccidity segmentally and a myelographic block several segments below the upper edge of function disturbance. In our case the myelographic block was between T_{11} and T_{12} and the upper border of hypalgesia was at T_8. The brown pigment observed in the cerebrospinal fluid in subdural, epidural, and intracerebral hematoma has been identified as methemoglobin. In subarachnoid bleeding the golden-yellow pigment in the cerebrospinal fluid is bilirubin.[13]

In a review of 10 cases[8] of acute nontraumatic spinal epidural hematoma straining effort was found to be a common precipitating event. Back pain was the first symptom in 6 of the patients. The interval from the onset of the first symptoms to the development of complete paraplegia varied from 20 minutes to 10 days; however, 50 per cent of the patients were completely paralyzed below the level of their lesion within 3 hours of the onset

of complaints. The shortest time interval from the development of paraplegia to surgical intervention was 4 days. Three of the 10 cases were fatal before surgical intervention. The location of the hematoma in 2 of these cases was in the upper cervical region. Recovery after surgery has varied from complete to none. Epidural hematoma in some cases does not cause complete spinal block and may not pursue a rapid course; in 1 patient, who had back pain for months after an injury, the syndrome of a ruptured intervertebral disk was simulated.[14]

Spontaneous spinal epidural hematoma is a rare disease. Of the 27 cases found in the literature, 1 patient had leukemia, 1 hemophilia, and including our case, 4 and possibly 5 had coumarin-induced coagulation defects. Thus, approximately one fourth of patients with this disease have had coagulation defects.

In the case presented, recurrent and progressive vertebral artery disease was the indication for anticoagulant therapy. There were no changes in dose during the last 8 months of therapy. The Quick prothrombin time was steadily in the "therapeutic" range except for 1 determination. In this setting an epidural hemorrhage developed in the absence of obvious trauma or localized disease. The only evident antecedent event was a possible Valsalva maneuver accompanying defecation. It is conceivable that as a result of increased venous pressure during this effort, one of the small valveless venules in the epidural space ruptured and that in the presence of her induced clotting defects the bleeding was not arrested.

In the last few years anticoagulant therapy has been used on a long-term basis in the prophylaxis of recurrent myocardial infarction[15–18] and the syndromes of insufficiency of the internal carotid, basilar or vertebral arteries.[19, 20] In these states the value of long-term anticoagulant therapy has been difficult to establish. The disease processes demonstrate marked, spontaneous variability. New clot formation, propagation, and dissemination play a variable role in the production of symptoms. Brief hypotension and transiently reduced cardiac output have been recognized as common triggers of ischemic symptoms with and without newly added vascular pathology.[21, 22] Clinical evaluation of the extent of vascular disease and clinical determination of progression are difficult. Unconscious bias and nonspecific effects have not been easily eliminated in studies of morbidity.[23] Double blind technics, which might indeed be helpful, are impractical.

The hazards of coumarin-induced coagulation defects include bleeding into the skin and subcutaneous tissue, mucous membranes, kidney, gastrointestinal and respiratory tracts, eye, pericardium, brain, and the coverings of the nervous system. In patients treated for weeks the incidence of major bleeding has been reported generally as 1 per cent, the incidence of any bleeding as 9 per cent.[24] The incidence of hemorrhage in patients maintained on anticoagulants for months to years is not as well established. In one series of more than 100 patients treated for 5 years the incidence was 42.1 per cent.[17] In other large series the incidence of hemorrhage has varied from 3 to 19 per cent.[15, 18] The possibility clearly exists that an increased incidence of bleeding after long-term administration may be due not only to the quantitative factor of the increased time of reduced Quick prothrombic activity but to the qualitative factor of the development of newly developing defects in coagulation after many weeks of administration.[25, 26]

The degree of hypoprothrombinemia necessary for clinically significant and safe interference with coagulation has been difficult to define. In clinical practice the "therapeutic" level has been accepted as that represented by a Quick 1-stage prothrombin time of approximately 2 to 3 times normal in seconds, roughly equivalent to 10 to 30 per cent of prothrombin activity. The Quick 1-stage prothrombin method reflects multiple factors influencing the rate of elaboration of thrombin and fibrin.[27] Coumarin derivatives have been shown to induce multiple coagulation defects.[25, 26, 28] Proconvertin, a factor stimu-

lating the conversion of prothrombin to thrombin, falls rapidly, as was observed in this case. The induced decrease of proconvertin is almost invariably greater in degree and earlier in time than that of prothrombin itself. A large fall in prothrombin may not be obtained for weeks. Deficiencies in plasma thromboplastin component (PTC) and Stuart factor are also induced. There is some evidence that there may be little antithrombotic effect from isolated proconvertin deficiency unless the deficiency is extreme, that the antithrombotic effect of Dicumarol may correlate with prothrombin deficiency, and that low levels of prothrombin and of PTC may favor hemorrhage.[26] A clear-cut distinction has been demonstrated between the coagulation defect and the antithrombotic effect of Dicumarol.[29] Further studies of factors influencing antithrombotic and hemorrhagic effects of anticoagulants are required. It is clear that the commonly used Quick prothrombin time yields information of a general nature, which has been helpful but may not be adequate. At "therapeutic" levels, a defect in coagulation is desired, which can interfere with gross intravascular thrombus formation and propagation and which nonetheless will not produce excessive bleeding from normal trauma.

The qualitative risks of anticoagulant therapy are clear. The occurrence of major bleeding appears unpredictable in an individual. Evaluation of the benefits and risks of long-term anticoagulants requires further studies on both sides of the question.

Summary

The occurrence of spinal epidural hematoma in a patient on long-term anticoagulant therapy of cerebral vascular disease has been reported.

The salient features of spinal epidural hematoma have been described.

Coumarin-induced defects in coagulation have been discussed.

Problems in the evaluation of long-term anticoagulant therapy have been raised.

Summario in Interlingua

Es reportate le occurrentia de hematoma spino-epidural in un patiente sub tractamento anticoagulatori a longe vista pro morbo cerebro-vascular.

Es describite le saliente characteristicas de hematoma spino-epidural.

Es discutite defectos coagulatori inducite per coumarina.

Es sublevate problemas in le evalutation de therapia anticoagulatori a longe vista.

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Pericardial Tamponade Following Percutaneous Left Ventricular Puncture

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A case of pericardial tamponade following percutaneous left ventricular puncture for the assessment of aortic stenosis is presented. Technical factors pertinent to the etiology of the complication are discussed. Emphasis is placed on the fact that current enthusiasm for percutaneous ventricular puncture should be tempered with an awareness of the associated complications that may ensue and require immediate definitive therapy in an environment well equipped for their management.

CREDIT for the first successful systematic study involving percutaneous left ventricular puncture in man must go to Ponsdomenech and Nunez,[1] who reported its use in 1951 for contrast visualization of the left ventricle and aorta. Following their initial study, a number of other investigators[2–4] have successfully employed percutaneous ventricular puncture for contrast visualization of the left ventricular chamber, aorta, and aortic and mitral valves.

Sir Russell Brock and his co-workers[5] in 1956 proposed and utilized percutaneous left ventricular puncture in the assessment of aortic stenosis. Recording synchronous left ventricular and brachial artery pressures proved to be a highly satisfactory means of establishing the systolic pressure gradient across the aortic valve for evaluation of the severity of aortic stenosis. Similar successful studies have been reported subsequently by other investigators.[6, 7]

In reviewing the available literature concerning percutaneous left ventricular puncture we were unable to find a single incidence of mortality in human subjects following this procedure. The collective series that we were able to cull from the cases reported in the literature to date totaled 348 (table 1).

The reported morbidity following this procedure has also been less than one would initially anticipate. Gregg and associates[2] reported a single incidence of ventricular fibrillation in their series that occurred following an injection of Diodrast almost directly into the coronary ostia. The patient underwent cardiac massage and had an uneventful recovery from the procedure. Syncope, pneumothorax, cardiac arrhythmia, hemoptysis, and renal pain and hematuria (presumably from an embolus) have also been reported following percutaneous left ventricular puncture.

The purpose of this report is to present a case in which cardiac tamponade developed following percutaneous left ventricular puncture. We wish to emphasize that, while the procedure is a useful and valuable adjunct in the objective evaluation of aortic and mitral valvular disease, the associated complications, when they occur, may require immediate definitive therapy in an environment well equipped for their management.

CASE REPORT

E. S. was a 31-year-old white male farmer who had had known heart disease since childhood. Approximately 1 year prior to admission to the University Hospitals he had been advised by his local physician that he should quit farming because of the severity of his heart disease. The progressive and incapacitating symptoms associated with his heart disease had subsequently caused his release from a number of jobs and, at the time of his admission, he was unable to get employment of any kind. Primary symptoms elicited in the history were those of dyspnea, palpitation, chest pain, and hemoptysis.

Minimal exertion was sufficient to initiate dyspnea, and the patient therefore attempted to move about slowly. Palpitation was frequently present at rest and was aggravated by excitement.

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TABLE 1.—*A Collective Series of 348 Cases of Percutaneous Left Ventricular Puncture and the Associated Mortality*

Author	Mortality	No. of cases
Brock et al.[9]	0	90
Green et al.[6]	0	25
Yu et al.[7]	0	30
Ponsdomenech et al.[1]	0	56
Gilman et al.[8]	0	86
Smith et al.[10]	0	32
McCaughan et al.[4]	0	29
Total	0	348

Since childhood, he had noted left anterior chest pain which occurred after severe exertion and frequently radiated to the left shoulder. This chest pain had been present almost constantly for 4 days prior to admission to the hospital. On several occasions in the past year, he had coughed up blood-tinged sputum but he denied the presence of a chronic cough or other symptoms of respiratory disease.

Physical examination referable to the cardiovascular system revealed a regular pulse of 116 per minute and a blood pressure of 124/95 in the upper extremities. There was a palpable left ventricular heave and an aortic systolic murmur with a split second sound which was normal or slightly accentuated. The peripheral pulses were equal, regular, and synchronous, but somewhat diminished in volume. The liver was palpable 3 to 4 cm. below the right costal margin on inspiration.

The chest x-ray revealed the pressure of left ventricular enlargement with dilatation of the ascending aorta. Calcification was not seen in the aortic valve area. The electrocardiogram revealed early left ventricular strain. Other laboratory studies were normal. The impression was one of aortic or subaortic stenosis requiring aortic valvotomy.

A few days after admission, right heart catheterization revealed no significant abnormal findings. It was then thought that percutaneous left ventricular puncture was indicated to substantiate the impression of aortic stenosis, to assess its severity, and to determine whether it was valvular or subvalvular in location.

Accordingly, the following day the patient was taken to the operating room where general anesthesia was induced using Surital supplemented with succinylcholine. After an endotracheal tube was introduced, anesthesia was maintained with nitrous oxide, oxygen, and occasional supplements of small amounts of Surital. A no. 18 gage needle was introduced percutaneously into the left ventricle, the point of entry being just lateral and inferior to the apex impulse, in the manner previously described by Brock.[5] The return of bright red blood and a recording of a ventricular pressure curve revealed that the catheter was in the left ventricle. The recorded ventricular systolic pressure of 125 mm. Hg was not what was expected from the patient's history.

An Afford catheter was then passed through the needle into the left ventricle and advanced across the aortic valve into the aorta. The pressure gradient across the valve also was not what was expected, being recorded as 25 mm. Hg. A pull back pressure tracing taken across the aortic valve revealed that the stenosis was valvular in location with no subvalvular component. It then became evident that technical problems in the measuring and recording apparatus were responsible for the low ventricular pressures recorded. Although these problems were rectified, a delay of 15 minutes ensued during which time the left ventricular needle was left in place. Gradually, during this interval, the patient developed a tachycardia of 120 per minute, with a fall in systolic blood pressure to 70 mm. Hg. The electrocardiogram revealed S-T depression consistent with myocardial ischemia. The needle in the left ventricle was immediately removed. Within 10 minutes there was no audible or palpable blood pressure although the electrocardiogram revealed a heart rate of 50 per minute. Auscultation over the precordium revealed barely audible heart sounds, and it was assumed that the patient had developed pericardial tamponade.

A 7-cm. incision was made immediately in the left fifth intercostal space anteriorly, and the chest was opened. The pericardium was seen to be distended, tense, and discolored by underlying blood. Normal vigorous myocardial contraction was not evident within the distended pericardium. A 4-cm. incision was made in the pericardium and the contained blood was allowed to escape. The remaining blood was aspirated from the pericardial space and totaled approximately 100 to 150 ml. Within 15 seconds following the evacuation of blood from the pericardium, vigorous myocardial contractions were apparent and the systemic blood pressure had returned to nearly normal levels. There was no evidence of bleeding from the puncture site in the left ventricular myocardium.

A Cournand needle was inserted into the apex of the left ventricle, and a shortened Afford catheter was passed again into the ventricular chamber. The left ventricular pressure was recorded as 190 mm. Hg. A needle was then placed in the left femoral artery and synchronous femoral arterial and left ventricular pressures were recorded. The

systolic gradient across the aortic valve was recorded as approximately 90 to 100 mm. Hg, which was consistent with the patient's clinical picture.

The postoperative course was uneventful. The intercostal catheter was removed on the first postoperative day and the patient was dismissed from the hospital on the third postoperative day ultimately to undergo aortic valvotomy with the aid of extracorporeal circulation.

Discussion

Percutaneous left ventricular puncture to assess the presence and severity of aortic stenosis is a satisfactory procedure which, however, may have significant complications. In a consideration of the etiology of the pericardial tamponade, as occurred in this case, one must reflect on the factors of (1) the site of puncture of the chest and left ventricle, (2) the size of the puncturing needle, and (3) the length of time that the needle remained within the heart.

Considerable discussion has centered about the choice of the proper site for left ventricular puncture as well as for pericardiocentesis. Those who prefer the subxiphoid route claim that this route allows the heart to be punctured at its apex where the chance of coronary artery laceration with associated pericardial tamponade is minimal. They also think that the incidence of pneumothorax is lessened by use of the subxiphoid route. The subxiphoid route has been used by Ponsdomenech,[1] Gilman,[8] Gregg,[2] and McCaughan.[4] Brock,[5] Green,[6] and Yu,[7] however, have preferred an intercostal space in close proximity to the apex beat and have encountered no untoward complications directly related to this site of needle puncture. Previous experience with the procedure had led us to believe that use of an intercostal space as a puncture site was quite satisfactory and allowed ready and direct introduction of the needle into the left ventricle. Although coronary artery laceration would be a reasonable explanation for the occurrence of pericardial tamponade, such was not the case in the patient reported here-in.

It seems reasonable that use of a large needle for puncturing the left ventricle would have more associated bleeding than would a smaller needle. We have used a no. 18-gage needle for percutaneous ventricular puncture. Our previous experience, and that of Brock[5] and Green,[6] utilizing the same size needles, had led us to believe that bleeding following left ventricular puncture by a needle of this size would not be of significance. Lehman and co-workers[3] in describing the technic utilized by Gilman, reported the use of a no. 15-gage needle in their series without untoward effects directly related to the needle puncture. Ponsdomenech,[1] in his original series, used a trocar with an external diameter of 1.7 mm. for ventricular puncture. Nevertheless, it seems appealing to us to incriminate the needle size as being at least contributory to the pericardial tamponade.

Just how much significance can be attributed to the time a puncturing needle remains within the heart is difficult to ascertain. Admittedly, in the case here reported, the puncturing needle remained within the left ventricle considerably longer than is desirable. One can reason that a relatively fixed, rather large bore needle, penetrating a beating ventricular chamber in which the systolic pressure was markedly increased could have enough associated bleeding to cause tamponade if left in place for a long enough period of time. We must therefore consider that the prolonged time factor was of significance in the development of the tamponade.

Lastly, consideration of the management of the tamponade is in order. Although a fair case might well be presented for aspiration of the pericardial space, we think that thoracotomy and pericardiotomy were the procedures of choice. Immediate thoracotomy allowed rapid and total evacuation of the pericardial space. It further allowed direct visualization of the myocardial puncture site. Had persistent bleeding from the puncture site or from a coronary artery laceration been present, it could have been repaired surgically. In addition, if the existing bradycardia had progressed to asystole, or if the pericardial decompression had not resulted in effective myocardial contraction, the thoracotomy would have allowed intermittent manual compres-

sion of the heart to maintain effective circulation.

Although percutaneous ventricular puncture has been performed by various investigators with the aid of local anesthesia only, the use of general anesthesia was certainly of considerable aid in the management of the complication of tamponade herein reported.

We urge strongly that percutaneous left ventricular puncture should be carried out by persons who are aware of and experienced in the management of the complications that may develop. Percutaneous left ventricular puncture should be performed only in an environment well equipped for the immediate and proper management of such complications.

Summary

A case is reported of pericardial tamponade that developed in association with percutaneous left ventricular puncture for the assessment of aortic stenosis. Possible etiologic factors and the management of the complication have been discussed.

Summario in Interlingua

Es reportate un caso de tamponade pericardial occurrente in association con percutanee punctura sinistro-ventricular effectuate in le evalutation de stenosis aortic. Es discutite le possibile factores etiologic e le tractamento del complication.

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Rupture of Aneurysm of Aortic Sinus of Valsalva Associated with Acute Bacterial Endocarditis

By HERSHEL JICK, M.D., P. JACK KASARJIAN, M.D., AND MORLEY BARSKY, M.D.

WHILE aneurysms of the aortic sinus of Valsalva are uncommon, the importance of the correct diagnosis has been emphasized by recent reports of successful surgical correction in patients with rupture of such an aneurysm.[1, 2]

A patient with a ruptured sinus of Valsalva associated with acute bacterial endocarditis recently seen at the Beth Israel Hospital, Boston, illustrates the problem of differential diagnosis in such instances.

J. H. (Beth Israel Hospital No. M84990), a 68-year-old white man entered the hospital on March 20, 1957, because of fever, chills, and dysuria for 3 weeks. Urine sediment was reported to have contained numerous white and red blood cells at the onset of the illness and sulfasoxazole (Gantrisin) and tetracycline therapy was instituted. During the next 2 weeks, the fever and dysuria subsided and therapy was discontinued. During the week prior to admission, however, the patient noted increased weakness, occasional chills, fever up to 102 F., and extreme dyspnea on slight exertion. A platelet count on the day of admission was reported as 18,000 per mm.^{3} and the hemoglobin was 9 Gm. per cent.

From 1941 to 1951 the patient received periodic phlebotomies with relief of mild symptoms of polycythemia vera. Between 1952 and 1954 increasing hepatosplenomegaly was noted, the hemoglobin and white blood cell count fell, and occasional metamyelocytes and myelocytes appeared in the peripheral blood. The diagnosis of myeloid metaplasia was tentatively made.

By August 1955, the platelet count was low, there were transient bleeding episodes and the hemoglobin was 7.6 Gm. per cent. Prednisone therapy was instituted. A chest film in December 1956 was unremarkable. The last known examination of the heart 4 weeks prior to admission indicated no change. A grade-II harsh blowing systolic murmur over the precordium, which had been present since 1941, was heard.

The patient on admission was acutely ill and in moderate respiratory distress. The blood pressure was 110/40 in both arms, the pulse was 90 and regular. Rectal temperature was 101.6 F.

There was cyanosis of the lips, and there were numerous ecchymoses over the abdomen and petechiae in the mouth. Crackling rales were heard at the right base. A strong thrill was felt maximally at the lower left sternal border in both systole and diastole. Grade-IV systolic and diastolic murmurs were heard over the entire precordium, loudest at the left sternal border in the fourth intercostal space. These murmurs radiated mainly to the right and downward. At times, the murmurs were continuous with a machine-like quality; at other times, there was a short silent period between the systolic and diastolic murmurs. First and second heart sounds were inaudible at the point of maximal intensity of the murmur. There was hepatomegaly, and the spleen was palpable 8 fingerbreadths below the left costal margin. Peripheral pulses were of the Corrigan type.

Repeated urinalyses showed intermittent hematuria and albuminuria. Hemoglobin on admission was 11 Gm. per cent but 4 units of packed cells were required over a 20-day period to maintain it there. White bood cell count was 5,200 with 80 per cent polymorphonuclear leukocytes, 5 per cent band forms, 11 per cent lymphocytes, 2 per cent monocytes, 1 per cent myelocytes, and 1 per cent metamyelocytes. Platelet count was 60,000 and reticulocyte count 3 per cent. Stool guaiac

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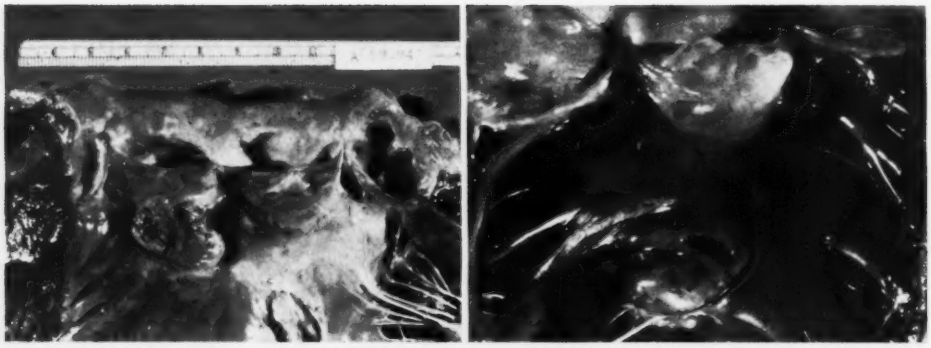

FIG. 1 *Left.* Aortic valve showing acute bacterial endocarditis. *Arrow* points to perforation of the right coronary aortic cusp.

FIG. 2 *Right.* Interior of right ventricle, showing pulmonary valve and aortic aneurysm bulging through interventricular septum. *Arrow* indicates a smooth-lined perforation.

on admission was negative; subsequently it was consistently 2+. The nonprotein nitrogen was 57 mg. per cent. Liver function tests showed parenchymal damage. Three blood cultures taken on admission were positive for *Staphylococcus aureus,* coagulase positive; subsequent blood cultures were negative. The venous pressure was 75 mm. of water.

Chest x-ray was consistent with pulmonary edema and slight enlargement of the heart. Electrocardiograms showed right bundle-branch block, first degree atrioventricular block, and left ventricular hypertrophy.

A regimen was started of bed rest, aqueous penicillin, 1,200,000 units intramuscularly every 4 hours, and streptomycin 0.5 Gm. intramuscularly twice per day, prednisone 12.5 mg. twice per day, and an ulcer diet. Lanatoside-C, 1.2 mg., was given over a 4-hour period followed by maintenance doses of digitoxin. One unit of packed red cells was also given.

By noon of the next day, the patient was afebrile and complained only of anorexia. Chest x-ray showed marked pulmonary congestion, which responded to a low-sodium diet and frequent injections of mercuhydrin. Positive blood culture reports of *Staph. aureus,* coagulase positive, supported the initial impression of bacterial endocarditis; penicillin and streptomycin were continued, since the organism was sensitive to these drugs. The most likely site of the rupture of the sinus of Valsalva if present was considered to be into the right ventricle or pulmonary artery rather than the right atrium or superior vena cava, since there was no pulsation of the neck veins.

During the first week, the patient continued to improve symptomatically. The blood pressures varied between 130/60 and 120/0. The murmurs changed only in minor degrees from day to day. On the ninth hospital day, a splinter hemorrhage was seen under the right thumbnail, and the aortic murmurs were louder. On the tenth hospital day, pulsation of the pulmonary artery was not seen during chest fluoroscopy. This was considered to be evidence against an aorta-to-pulmonary artery fistula.

On the seventeenth hospital day, the patient suddenly developed dyspnea at rest and marked orthopnea, and physical signs consistent with pleural effusion were noted at both lung bases. Digitoxin dosage was increased and ammonium chloride and acetazolamide (Diamox) were added to the diuretic regimen. On the twenty-first hospital day, 1,200 ml. of straw-colored fluid were removed from the right pleural space and on the following day 500 ml. were removed from the left pleural space. Following these procedures there was some relief of dyspnea; however, the fluid reaccumulated in each pleural cavity and required removal on the twenty-sixth hos-

ital day. At 3:30 a.m., on the twenty-sevnth hospital day, the patient died suddenly, aving remained afebrile since the first hosital day.

Pathologic Examination

At autopsy, the heart was slightly enlarged eighing 410 Gm. There was an aneurysm of he right coronary sinus of Valsalva, 3.5 cm. eep and 2.5 cm. in greatest diameter (figs. and 2). Most of the lining of the aneurysm, ncluding the right coronary cusp, was yellowsh and ragged, but a portion was smooth. There were 2 communications between the aneurysmal sac and the right ventricle, each about 0.4 cm. in diameter. One of these, within the ragged zone, had an irregular edge (fig. 3*c*); the second, within the smooth area, had a regular smooth edge (fig. 2). There was also a communication with the left ventricle through the right coronary cusp, measuring 0.5 cm. in diameter (fig. 3*b*). The commissure between the right and noncoronary cusps was excavated, yellowish, and ragged. On section, this alteration was seen to extend upward in the subepicardial tissue and into the right atrium, where it presented as a nodule immediately above the posterior commissure of the tricuspid valve.

Microscopic examination revealed necrotizing inflammation in the aneurysm, the right coronary cusp, and the abnormal commissure, with extension into the right atrium and the adventitia at the root of the aorta. These areas contained numerous inflammatory cells and many colonies of cocci, embedded in a fibrin mesh. The grossly smooth part of the aneurysm showed a fibrous wall with little active inflammation. The entire picture was consistent with an acute bacterial endocarditis in an aneurysm of the sinus of Valsalva with several perforations. It could not be determined whether the aneurysm was congenital or was an erosive aneurysm caused by the acute bacterial endocarditis.

Other pertinent findings included an enlarged liver and spleen (2,400 and 1,120 Gm., respectively) which showed myeloid metaplasia. The bone marrow was hyperplastic. An occasional focus of hematopoiesis was noted in the right kidney. The lungs were acutely congested and edematous. There was obstructive benign prostatic hypertrophy, with bilateral nephrolithiasis and cystolithiasis. There was stenosing arteriosclerosis of the ostium of the right renal artery associated with an atrophic right kidney (70 Gm.) and compensatory hypertrophy of the left kidney (270 Gm.). Petechiae were present in the left kidney, bladder, bowel, and skin of the back, and there were large ecchymoses on the extremities.

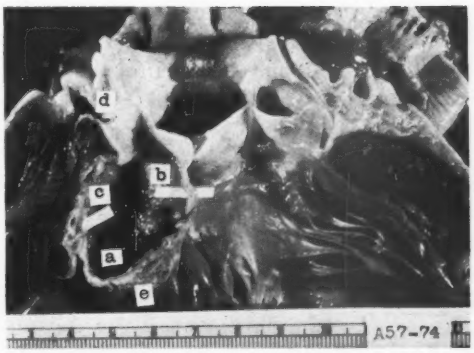

Fig. 3. Heart sections through aneurysm. (*a*) necrotic wall of aneurysm, (*b*) perforation into left ventricle, (*c*) rough-lined perforation into right ventricle, (*d*) right coronary artery, and (*e*) interventricular septum.

Cultures of the aortic valve lesion grew out coliform bacilli, *Bacillus subtilis,* and coagulase negative *Staph. albus;* these were considered contaminants. Culture of heart blood taken at autopsy was sterile.

Discussion

The sinuses of Valsalva are 3 small dilatations in the wall of the aorta immediately above the aortic valves. They are in close relation to all of the cardiac chambers, particularly the right atrium and right ventricle.

Aneurysms of a sinus of Valsalva are either congenital or acquired. Congenital aneurysms are thought to be due to developmental defects in either the aortopulmonary segment or the elastic tissue of the aortic sinuses. Jones and Langley[5] list the following criteria for differentiating the 2 types. In the congenital type, the aneurysm (1) is confined to the

right coronary sinus and adjacent two thirds of the noncoronary sinus; (2) is usually small; (3) commonly ruptures into the right ventricle or right atrium; (4) remains intracardiac; (5) is usually associated with other developmental defects. In the acquired type, the aneurysm (1) may arise from any sinus; (2) tends to extend upward; (3) is often extracardiac; (4) cardio-aortic fistulae are rare; (5) congenital cardiac defects are rare; (6) it is always associated with acquired heart disease, usually syphilis or bacterial endocarditis.

Diagnosis of nonperforated aortic sinus aneurysm is difficult. Falhot and Thomsen in 1953 described a case of unruptured congenital right aortic sinus aneurysm diagnosed by retrograde aortography.[6] Steinberg and Finby[7] made the diagnosis of unruptured aortic sinus aneurysm in 16 cases by angiocardiography. Six were thought to be congenital: 3 were patients with arachnodactyly and 3 were associated with coarctation of the aorta. In 9 of the remaining 10 cases, the aneurysm was due to syphilis. Steinberg suggested that the only clue to diagnosis on physical examination is a grade-III to IV systolic murmur over the heart, especially to the left of the sternum.[11]

Perforation of an aneurysm is ordinarily accompanied by sudden intense dyspnea, sometimes associated with chest pain, especially on minimal exertion; increase in pulse pressure; sudden appearance of continuous or "to-and-fro" murmurs usually at the fourth intercostal space to the left of the sternum.

Diagnostic methods which have been used to establish the diagnosis include cardiac catheterization[3, 8, 9] and surgical exploration.[10]

In our case, the diagnosis of ruptured aortic sinus of Valsalva into the right ventricle was strongly suggested by the history of sudden onset of extreme dyspnea on minimal exertion, the wide pulse pressure suggesting a lesion at or above the aortic valve, the finding at the lower left sternal border of a machinery murmur which radiated mainly to the right and downward, and the known association of acute bacterial endocarditis with this condition. Absence of facial edema and other features of a superior mediastinal syndrome was evidence against a fistula between the aorta and superior vena cava. Absence of pulsation in the pulmonary artery was evidence against rupture into that structure. Absent cervical or peripheral venous pulsations were evidence against rupture into the right atrium.

Other conditions considered in the differential diagnosis were patent ductus arteriosus and aortic stenosis and regurgitation secondary to bacterial endocarditis. These diagnoses were considered unlikely on the basis of the character, location, and radiation of the murmurs.

It cannot be ascertained whether the aneurysm was congenital or acquired. In favor of a congenital origin are presence of a systolic murmur over the precordium for at least 15 years, presence of the aneurysm in the right aortic sinus, and rupture of the aneurysm into the right ventricle.

As is illustrated by our patient, the course of the disease is almost always rapidly deteriorating with most patients dying of intractable congestive heart failure within 6 months.

In view of a recent case report of successful diagnosis and surgical treatment of rupture of an aortic sinus aneurysm,[1] surgical correction was briefly considered in the case presented here, but the idea was abandoned because of the patient's poor general condition.

Summary

A case of ruptured aortic sinus of Valsalva aneurysm secondary to acute bacterial endocarditis is presented. In diagnosis of this entity emphasis is placed on the character, location, and radiation of the murmur. Importance of correct diagnosis is mentioned, since in some cases surgical correction may be carried out.

Summario in Interlingua

Es presentate un caso de ruptura de un aneurysma del aortic sinus de Valsalva,

secundari a acute endocarditis bacterial. In le diagnose de iste entitate, le accento dabe esser ponite super le studio del character, del location, e del radiation del murmure. Le importantia del obtention de un diagnose correcte es augmentate per le facto que in certe casos un correction chirurgic pote esser effectuate.

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Quotation from "ART AND LIFE"

Leonardo da Vinci

Italian painter, sculptor, and scientist; 1452-1519

The supreme misfortune is when theory outstrips performance.

Poor is the pupil who does not surpass his master.

Nature never breaks her own law.—*Note Books.* Trans. Edward McCurdy. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

A Case of Abnormal Cardiac Position (Levoposition)

By G. G. Rowe, M.D., and L. W. Paul, M.D.

ALTHOUGH dextroposition (dextroversion, uncomplicated isolated dextrocardia) is a well accepted anatomic configuration of the heart[1, 2], it is believed that displacement of the heart into the left hemithorax to the degree here reported is an anatomic abnormality that has not been described previously.

The patient was a 22-year-old white man who complained of dyspnea on exertion. He had known for many years that his heart was "not normal" and had been told repeatedly by physicians to limit his activity. He had noted for the first time when he was in high school that he became more dyspneic on exertion than his friends and although he could work all day at a steady rate, if he tried to hurry he developed symptoms. He believed that his fingernails had become cyanotic on occasions and he noted palpitation on exertion. It was difficult to be sure how much of his disability was induced by his heart and how much was iatrogenic.

Physical examination revealed the chest wall to be of normal configuration without pectus excavatum. A cardiac impulse of normal character was located between the anterior and lateral axillary lines on the left. There was a grade II to III pulmonic systolic murmur and a widely split pulmonic second sound. Chest roentgenograms (figs. 1 and 2) revealed that the gastric air bubble was on the left, and the heart was greatly displaced into the left hemithorax, lying on the diaphragm.

Laboratory examination revealed normal urine and peripheral blood. An electrocardiogram (fig. 3) showed peaking of the P waves in the precordial leads. The electrocardiographic position was indeterminate. There was an rSr′ pattern in V_2 and the T waves were low in V_4 and V_5 and inverted in V_6. No specific interpretation of this tracing could be made.

Cardiac catheterization was done in order to reassure the patient, since it was considered that he had a normally functioning heart, but it was also believed that he could not be reassured effectively without having some objective demonstration of cardiac normality. The pulmonary arterial blood pressure was 26/11 with a mean of 16 mm. Hg. The mean pulmonary artery wedge pressure was 13 mm. Hg and presented V waves 9 mm. Hg in height. Right ventricular pressure was 30/-1 with an end diastolic of 7. Femoral arterial blood pressure was normal as was systemic arterial oxygen saturation. By oximetry there was no evidence of any intracardiac shunt. The pulmonary wedge pressure was higher than we usually see in normal persons.

The patient was reassured that his heart was anatomically displaced but physiologically satisfactory.

Discussion

Displacement of the heart secondary to disease in the thorax is not part of the present discussion, since the lesion described occurred in an otherwise normal individual. For lack of demonstrable related thoracic disease the displacement is assumed to have been congenital in origin even though there was no evidence of anomalous pulmonary venous connection as has been described in some cases with dextroposition of the heart,[3, 4] nor of any other congenital cardiac defect. Dextroposition is well known to occur without associated congenital defects,[1, 2] so that the absence of the associated congenital lesion need not militate against the assumption of congenital origin for this case of "levoposition."

Although the cause of cardiac malposition is unknown, it is said that the embryologic abnormality that produces it must take place in the second week of fetal life when normal

From the Departments of Medicine and Radiology and the Cardiopulmonary Laboratory, University of Wisconsin, Madison, Wis.

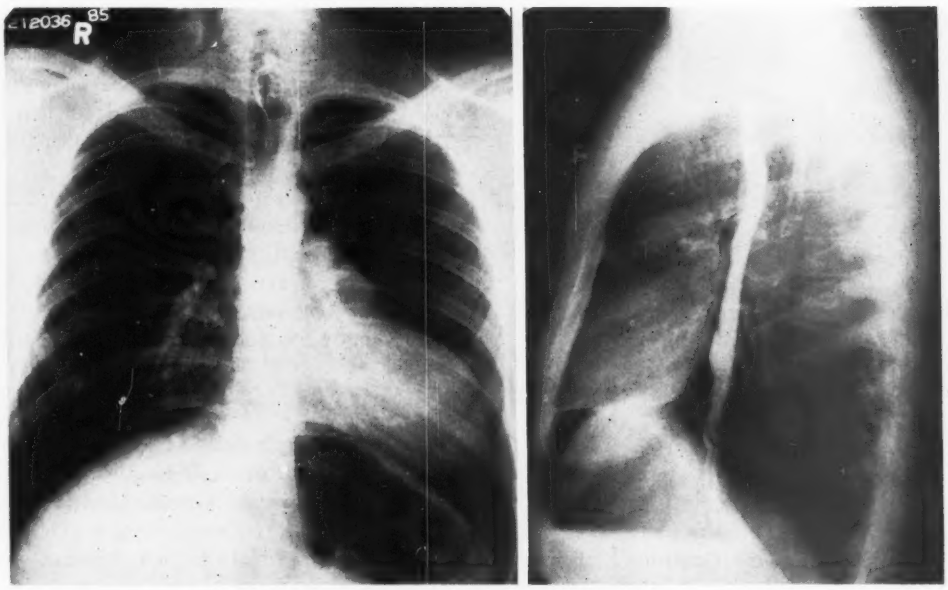

FIG. 1. Posteroanterior and lateral roentgenograms of the chest. The displacement of the heart is well shown in the frontal projection with the mass of the left ventricle almost completely separated from the shadow of the diaphragm. The heart is rotated in a counterclockwise direction.

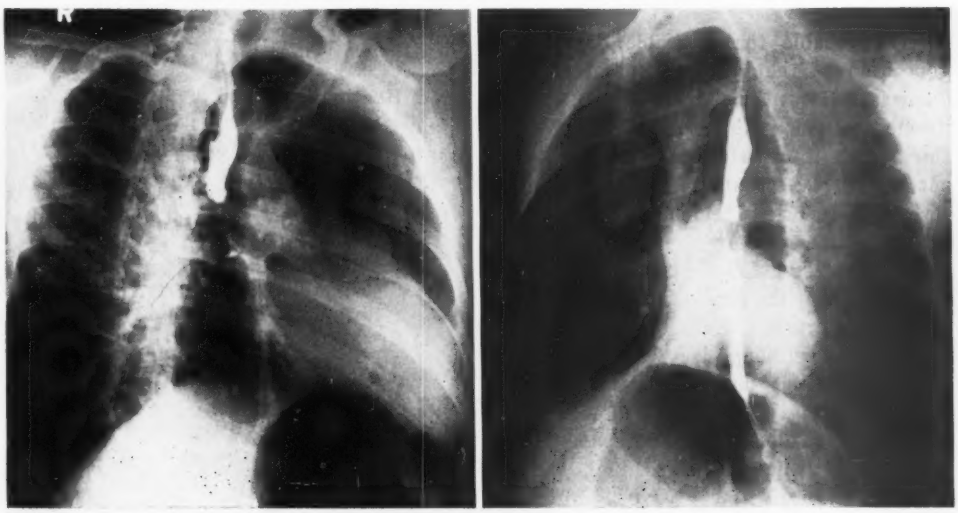

FIG. 2. Right anterior and left anterior oblique roentgenograms with barium in the esophagus. The left ventricle projects posteriorly more than in the normal. The unusual prominence of the pulmonary artery is noteworthy.

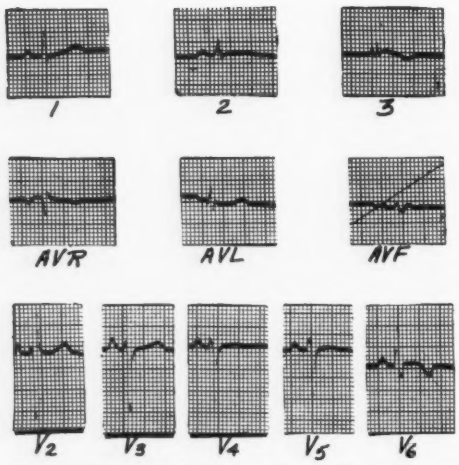

FIG. 3. Electrocardiogram of the patient with "uncomplicated levoposition" of the heart.

rotation should occur.[2] Dextroposition of the heart seems to be produced by a reversal of the normal rotation,[2] and is characterized by displacement of the heart toward the right, producing a radiographic picture of dextrocardia but without inversion of the cardiac chambers and without the electrocardiographic pattern of dextrocardia.[1] Dextroposition is much more common than is levoposition of the degree described here. It is, of course, entirely probable that variable degrees of levoposition of the heart exist and are accepted as within normal limits until such an extreme position as that in the present case occurs. Such interpretation of cardiac positions might well account for the discrepancy between the reported incidence of the 2 types of malposition.

It is of considerable interest to observe how far from normal the cardiac position may be without distorting the electrocardiogram fundamentally, although it is known that anatomic and electric positions are frequently not related.[5] The present case affords some measure of the degree of discrepancy that may occur. Cardiac catheterization, by excluding significant pathologic lesions, afforded this patient considerable relief from anxiety about his heart.

SUMMARY

Dextroposition and levoposition are both believed to be forms of cardiac malposition that arise in early fetal life. It is believed that this is the first case of levoposition reported.

When cardiac positions are grossly abnormal, special investigations are required to establish normality of cardiac function, since usual criteria for physical findings, electrocardiographic data, and radiographic determination of size and shape may not be applicable.

SUMMARIO IN INTERLINGUA

Es opinate que dextro- e levoposition del corde es ambes formas de malposition cardiac que ha lor origine in le prime phases del vita fetal. Le presente caso pare esser le prime caso levoposition reportate in le litteratura.

In casos de grossier anormalitate del position cardiac, investigationes special es requirite pro testar le normalitate del functiones del corde, proque le criterios usual—le constatationes physic, le datos electrocardiographic, le determinationes radiographic de dimension e conformation—non es necessarimente applicabile.

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CLINICAL PROGRESS

Bacterial Endocarditis in the Antibiotic Era

With Special Reference to the Later Complications

By WILLIAM L. MORGAN, M.D., AND EDWARD F. BLAND, M.D.

IN 1944 Loewe and his associates demonstrated the effective use of penicillin in the treatment of bacterial endocarditis.[1] During the ensuing decade and a half, 228 patients with this disease have been treated at the Massachusetts General Hospital. The present report concerns primarily the outcome of therapy in this group with particular reference to the fate of those who survived their active disease. It also emphasizes certain syndromes and delayed complications peculiar to the healing process. As a reminder of the relentless deteriorating course that prevailed before the antibiotic era, a brief review of the earlier contributions that established this disease as a clinical entity and prepared the way for successful therapy is included.

In 1852 Kirkes first clearly attributed systemic emboli to vegetations on heart valves,[2] but similar cases actually had been described as early as 1707 by Lancisi and later by Senac, Morgagni, and others.[3] It was Kirkes, however, who provided the impetus to study ulcerative endocarditis at the time when pathologic investigation was foremost and bacteriology was still in its infancy.

By 1870, Winge and Heiberg had visualized microorganisms in valvular vegetations.[4, 5] Wilkes had associated arterial pyemia with endocarditis, pointing out that such a febrile illness might be mistaken for ague or miasmatic fever,[6] and Lancereaux, Leyden, and Secondi had each given clear clinical descriptions of the disease.[7-9] By 1886, Wyssokowitsch had isolated *Stapylococcus aureus* from a case of ulcerative endocarditis and had produced the disease in dogs.[10]

In 1885 appeared the important contribution of William Osler. He presented in the *Gulstonian Lectures* an analysis of 209 cases of malignant endocarditis and gave a description of its pathologic features.[11] He recognized that healed rheumatic valvulitis was a frequent precursor and the presence of microorganisms in the vegetations a constant feature of this disease. Subsequently in 1908 he described the "chronic" cases and at that time called attention to the *"nodosités cutanées éphémères"* which bear his name.[12]

By the turn of the century the nature of the organisms causing bacterial endocarditis had become known and the diagnostic technic of blood culture had come into use.[3, 13-15] While opinions differed as to the classification of the gram-positive coccus, Schottmüller in 1910 identified it as a streptococcus of the "viridans" type.[16] At the same time Löhlein described the focal embolic nephritis characteristically found post mortem,[17] which Horder had labeled the "flea-bitten kidney,"[18] a feature more fully discussed by Baehr in 1912.[19] Libman, who is credited with having named the disease subacute bacterial endocarditis, called attention to an occasional patient whose lesions healed spontaneously.[20]

By the end of the second decade of this century the clinical concept of this disease had been crystallized.[21, 22] Therapy, however, was universally unsuccessful, although Blumer predicted that "chemotherapy might in the future be developed to a degree permitting

From the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Mass.

TABLE 1.—*Bacterial Endocarditis (1944-1958) 228 Cases*

	Cured	Died	
		Treated	Unrecognized
Acute (53)	8	13	32
Subacute (175)	119	31	25

of the elimination of these organisms from the body."

In the 1920's and 1930's clinical studies emphasized the frequency of bacterial endocarditis in rheumatic and congenital heart disease,[23-27] and pathologic studies were concerned with further detailed descriptions of the cardiac and systemic manifestations[28-34] and the mechanism of valvular infection.[35-37]

During this period an occasional encouraging instance of surgical cure was reported. Thus in 1935 Hamman and Reinhoff, by excision of an infected arteriovenous aneurysm of the external iliac, cured a case of subacute endarteritis and septicemia,[38] and Touroff in 1940 described a patient with an infected patent ductus arteriosus who recovered after ligation of the ductus.[39]

With the advent of sulfonamide therapy in 1938, the promise of definitive treatment appeared near realization, but results proved disappointing. Lichtman's review in 1943 of 2596 cases in the literature revealed recovery of only 4 to 6 per cent of the patients treated with sulfonamide, alone or in combination with heparin or hyperthermia.[40] Prior to this therapy approximately 1 per cent of patients had recovered spontaneously. Anticoagulants which were used in conjunction with the sulfonamides in 1939[41] were soon abandoned because of the added risk of cerebral hemorrhage, presumably secondary to embolism.[42, 43]

In 1944, after decades of disappointment, a new and brighter era began. Very soon after the introduction of penicillin it became apparent that nearly 3 out of 4 of the victims of this heretofore fatal disease could be rescued.[44-46] Now that almost 15 years have elapsed, both the immediate and the ultimate fate of patients with bacterial endocarditis can be viewed in helpful perspective.

THE PRESENT STUDY

The 228 patients who form the basis for this report comprise all cases with bacterial endocarditis admitted to the Massachusetts General Hospital since 1944. The criteria for diagnosis were a clinical picture compatible with bacterial endocarditis and at least 2 positive blood cultures, or a pathologic diagnosis post mortem. There were 15 of 11 successfully treated patients who had negative blood cultures but presented the characteristic clinical features of this disease.

The 228 patients may be divided for convenience into 3 major groups (table 1): (1) those with acute bacterial endocarditis (53 cases); (2) those with subacute bacterial endocarditis who died during hospitalization (56 cases); and (3) those with subacute bacterial endocarditis treated successfully (119 cases).

The patients with acute bacterial endocarditis were somewhat older than the subacute cases, with an average age of 55 years, ranging from 8 months to 85 years and equally divided as to sex. *Staphylococcus aureus*, the predominant organism, was found in 31 instances (60 per cent).*

In nearly one half (25) of the acute cases there was no apparent preexisting cardiac disease or defect. Rheumatic valvular disease was found in 18 instances, calcific aortic stenosis in 6, bicuspid aortic valve in 2, syphilitic aortitis in 1, and a ventricular septal defect in 1.

Of the 175 patients with subacute bacterial endocarditis, there were 96 males and 79 females; the ages ranged from 3¼ to 96 years, with an average of 42. In the 119 cured cases, rheumatic heart disease was present in 105 and congenital heart disease in 14. *Streptococcus viridans* was isolated in 87 (73 per cent).† The usual treatment was parenteral

**Staphylococcus aureus* 31, Pneumococcus 9, no organism 6, *Bacillus coli* 2, and 1 each of *B. proteus*, α-hemolytic streptococcus, β-hemolytic streptococcus, *Hemophilus influenza*, and brucella.

†*Streptococcus viridans* 87, *Staphylococcus albus* 2, β-hemolytic streptococcus 2, Enterococcus 2, *Staphylococcus aureus* 1, *Hemophilus influenzae* 1, diagnosis post mortem 8, and negative cultures in 15.

penicillin for at least 3, often for 4 weeks or longer and penicillin combined with other antibiotics in special instances.

Forty-eight of the 56 patients who died had postmortem examination. Twenty-nine of them were afflicted with *Streptococcus viridans;* in 18 patients no organism was isolated.* Rheumatic heart disease was present in 38 of the fatal cases, whereas in 8 instances there had apparently been no antecedent valvular disease as far as clinical history or postmortem examination could disclose.†

Acute Bacterial Endocarditis

Only 8 of the 53 patients with acute bacterial endocarditis (15 per cent) survived hospitalization. The cause of the high mortality is partially explained by the fact that the diagnosis was made during life in only 2 patients. The reasons for failure of diagnosis were as follows. In 19 instances the presence of endocarditis was masked by the signs of overwhelming infection elsewhere, notably by pneumonia, meningitis, or peritonitis (11 of these infections were postoperative). Furthermore, there were 11 patients who did not survive long enough to permit a diagnosis. Of the 21 cases in which the disease was recognized before death, therapy was inadequate in 8, since only a few days elapsed between diagnosis and death. Of the remainder, 4 were given too low a dose by present standards, 2 died of resistant infection despite high antibiotic dosage, 1 died of a myocardial abscess with compression of a coronary artery, and 6 survived. The 2 additional patients who survived are of special interest. The acute endocarditis, unrecognized at the time in both instances, had been cured with treatment of a severe pulmonary infection, but months later postmortem examination revealed the healed bacterial endocarditis that had been unsuspected during the acute illness.

Streptococcus viridans 29, Enterococcus 3, *Staphylococcus aureus* 2, *Staphylococcus albus* 1, *Bacillus* 2, *B. pyocyaneus* 1, no organism 18.

†Rheumatic heart disease 38, calcific aortic stenosis 4, tetralogy of Fallot 2, biscuspid aortic valve 2, transposition and bicuspid pulmonary valve 1, pulmonary stenosis 1, and no valvular disease 8.

Table 2.—*Fatal Complications during Bacterial Endocarditis (92 Postmortem Cases)*

	Acute bacterial endocarditis	Subacute bacterial endocarditis
Systemic emboli		
Cerebral	16	13
Major coronary	4	5
Mesenteric	2	1
Other major	4	2
Mycotic aneurysms		
Cerebral with rupture		3
Cerebral without rupture		1
Aortic root with rupture		2
Aortic root without rupture		3
Coronary with rupture	1	
Mitral valve	1	
Ruptured heart valves		
Mitral or chordae tendineae	3	9
Aortic cusps	5	4
Mitral and atrial septum	1	
Glomerulonephritis with clinical uremia	1	5
Splenic rupture		1

Postmortem examination was performed on 44 patients (table 2). In contrast to the findings in the subacute cases, many emboli were septic and the valve damage was more acute, but mycotic aneurysms and glomerulonephritis were less frequent, probably because of the shorter duration of the disease.

In the 8 survivors *Staphylococcus aureus* was the responsible organism in 5 instances, and a pneumococcus in 3. The latter infections were successfully eradicated by 2 to 4 million units of penicillin a day over a 3- to 4-week period. However, in the staphylococcal cases very large doses of penicillin were used, from 20 to 60 million units a day for 5 weeks, combined with other antibiotics such as chloramphenicol and erythromycin or, in the later cases, vancomycin.

Three of the survivors have subsequently died: 1, in whom a perforated mitral valve was found post mortem, after 6 months of progressive congestive failure; 1 after 17 months of progressive congestive failure; and the third 20 months after cure, with cerebral emboli complicating a mitral valvulotomy. Five patients are living at 3, 4, 17, 34, and

TABLE 3.—*Major Factors as a Cause of Death during Subacute Bacterial Endocarditis*

Series	Total no. patients	Number dead	Percentage dead	Congestive failure	Arterial embolism	Uremia	Cerebral or other hemorrhage	Resistant infection
Anderson and Keefer (1948)	457*	149	32	33	22	3	5	53
Friedberg (1950)	148	50	34	29	13	6		6
Cates and Christie (1951)	408†	108‡	24	50	13	14	10	25
Present (1958)	175	56	32	32§	21	5	6	

*Cases of non-hemolytic streptococcus subacute bacterial endocarditis with one or more treatment courses, collected from various hospitals in the United States.

†Based on an analysis of 408 patients with positive blood cultures from 14 treatment centers in Great Britain.

‡Cases dying during treatment and within 1 month.

§Includes 13 with valve rupture.

60 months after cure of the acute infection.

In comparison the series reported by Anderson and Keefer is of special interest.[47] They collected from the literature, up to 1948, 116 cases of staphylococcal endocarditis treated with antibiotics. The mortality was 77 per cent. Subsequently others have recorded a slightly more encouraging outcome with approximately a 50 per cent survival rate,[48, 49] but the most recent report (1958) by Shubin and his collaborators indicated a 74 per cent death rate in 27 cases.[50]

As to therapy, Finland (1958) recommends that endocarditis caused by a resistant staphylococcus be treated by 2 antibiotics to which the organism is sensitive, initially in the maximum tolerated dose by the parenteral route, with treatment continued for 6 weeks. A change to the oral route and lower dosage is advised only after bacteremia, fever, and acute symptoms have subsided. If tolerance develops, the dose should be increased to the maximum tolerated or the antibiotics should be changed.[51]

SUBACUTE BACTERIAL ENDOCARDITIS UNSUCCESSFULLY TREATED

Fifty-six of the patients with subacute bacterial endocarditis died before leaving the hospital (32 per cent). Congestive heart failure was an important cause of death in 31 of these patients. It can be seen from the postmortem findings of 48 of these cases that recent severe endocardial damage superimposed on preexisting heart disease of considerable degree was usually the determining factor (table 2). The immediate cause of death in one half of the cases was an embolus to a major systemic vessel or rupture of either a mycotic aneurysm or a valve cusp. Embolic myocardial infarction occurred in 5 instances, and this together with focal myocardial injury was probably an important factor in congestive failure and death in 14 of the 48 postmortem cases.

It is possible that many of these severe complications could have been prevented by earlier and more vigorous treatment, since the diagnosis was not suspected in 25 patients and 7 other patients died within a few days after diagnosis and before therapy could be effective. In general the reasons that the diagnosis was not suspected or established were as follows: hospitalization for only a few days; mistaking a complication (such as myocardial or cerebral infarction) for the primary disease; masking of symptoms by antibiotics employed for localized infection elsewhere; negative cultures; and absence of fever. Ten patients in the early days were given too small a dose by present standards.

The experience of others has been similar to that in the present series (table 3). A mortality of 32 per cent was recorded in Anderson and Keefer's collected statistics on a series of 457 patients with non-hemolytic streptococcus endocarditis.[47] Friedberg's mortality rate was 34 per cent in 148 patients,

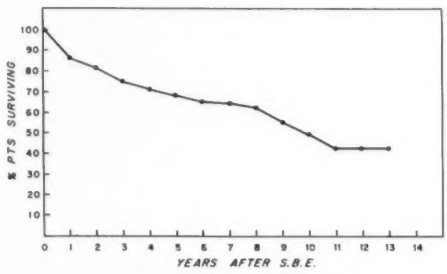

FIG. 1. Survival after subacute bacterial endocarditis.

In his study inadequate therapy was explained by negative cultures in 19 instances, resistant organisms in 8, and diagnostic errors in 8. The commonest cause of death in his 50 fatalities was congestive heart failure in 29, cerebral embolism in 13, uremia in 6, and persistent infection in the remainder. In a combined study of 408 patients assembled from 14 centers in Great Britain, Cates and Christie found a mortality of 24 per cent during treatment or within a month thereafter.[44]

SUBACUTE BACTERIAL ENDOCARDITIS SUCCESSFULLY TREATED

Of the patients with subacute bacterial endocarditis 119 (68 per cent) were treated successfully and were discharged from the hospital clinically well. If the 25 cases are excluded in which the disease was not recognized before postmortem examination, 79 per cent recovered of those actually treated. All 119 cured patients have been followed up to the present except for a single patient treated in 1948 who is "lost." The present state of health in each instance has been determined by hospital examination or by consultation with the patient or his physician. Figure 1 indicates the fate and duration of follow-up of the 119 survivors, and table 4 presents the detailed statistical analysis of the clinical data based on the method of Merrell and Shulman.[52] It can be seen that 60 patients have been followed for 5 years with a 70 per cent survival rate, and 23 patients for 10 years with a 50 per cent survival. The annual death rate in the present study averages 5 to 6 per cent.

TABLE 4.—*Follow-Up of 119 Patients after Subacute Bacterial Endocarditis**

Years after subacute bacterial endocarditis	No. of patients observed at a given year	No. of patients living but withdrawn from series in next yearly interval	No. of patients dying in next yearly interval	Estimated proportion of persons surviving to a given year who: die before next yearly interval	survive next yearly interval	Percentage of patients surviving
0	119†	4	16	0.137	0.863	100
1	99	0	5	0.051	0.949	86.3
2	94	3	8	0.087	0.913	81.9
3	83	9	4	0.051	0.949	74.8
4	70	8	2	0.030	0.970	71.0
5	60	6	2	0.035	0.965	68.9
6	52	4	1	0.020	0.980	66.5
7	47	7	1	0.023	0.977	65.2
8	39	3	5	0.133	0.867	63.7
9	31	5	3	0.105	0.895	55.2
10	23	3	3	0.140	0.860	49.4
11	17	5	0	0	1.000	42.5
12	12	9	0	0	1.000	42.5
13	3	3	0	0	1.000	42.5

*Based on Life Table statistical analysis,[52] at the suggestion of Dr. Jane Worcester, Harvard School of Public Health.

†The patient lost to follow-up is included.

These findings are in accord with those of Cates and Christie in their 4-year follow-up survey of collected cases, in which they found that after the first 6 months there was a low death rate of 4 per cent per annum. Several recent reports have presented follow-up data on patients with treated bacterial endocarditis, but as yet very few series include patients followed 10 years or longer,[44, 46, 53-61] Thus in over 700 of these patients from the literature described as successfully treated, only 52 have been followed 5 or more years and only 17 to 10 or more years.

THE FATE OF PATIENTS WITH HEALED BACTERIAL ENDOCARDITIS

It has become increasingly clear with continued observation that even though therapy has been successful, a variety of delayed complications may occur in subsequent years. In

particular, further valve deformity associated with the healing of bacterial endocarditis may play a determining role in the patient's later course.

There were 50 patients who survived subacute bacterial endocarditis but later succumbed, and a considerable number of patients were never quite well again. The prime cause of disability and death appeared to be slowly progressive heart failure in 21 instances, sudden death complicating severe aortic regurgitation in 4, cerebral vascular accident in 4, pulmonary embolism in 3, uremia in 3, subsequent acute bacterial endocarditis in 2, unassociated disease in 3; it was unknown in 10 cases.

The pathologic findings in 17 of the 50 patients who were successfully treated but later died serve to emphasize the importance of certain delayed clinical syndromes (table 5). Twelve of these patients showed severe valvular deformity, principally from healed subacute bacterial endocarditis which in turn resulted in slowly progressive congestive heart failure. Two patients revealed no recognizable residual vegetations, and 3 others had only small healed vegetations. The noteworthy features of healed endocarditis in this series are as follows:

Limitation of Activity. There are 68 living patients: 4 have been in congestive failure and 4 others have minor limitation; the remaining 60 are normally active. If all the cases that survived subacute bacterial endocarditis are considered, 42 of the 119 were ultimately in congestive heart failure (36 per cent). Kerr likewise has estimated that of the patients surviving treatment, one-sixth to one-third will have residual impairment.[62]

Recurrence of Bacterial Endocarditis. Ten patients had a recurrence of bacterial endocarditis 6 months to 10 years after the initial episode (table 6). All were readmitted to the hospital with 2 or more positive blood cultures and were successfully treated, except for 2 patients with *Staphylococcus aureus* endocarditis who died. One of these fatal cases had acute vegetations at the perforation site (presumably old) of an aortic cusp, and the other developed acute bacterial infection following mitral valvulotomy. This recurrence figure of 8.5 per cent is higher than that in the literature, which is quoted as 2 to 4 per cent,[44, 46] but the longer duration of follow-up here, as compared with earlier reports, seems an adequate explanation for this discrepancy.

Severe Aortic Incompetence. Sixteen of the 119 cured patients had severe aortic incompetence characterized clinically by free regurgitation. In 8 instances subacute bacterial endocarditis either caused or aggravated the degree of valvular insufficiency. Nine patients are living at the latest follow-up, 5 of whom are well compensated. Four of the 16 have angina pectoris on effort, and 5 have undergone surgery with insertion of a Hufnagel valve. Four patients came to postmortem examination, and the findings indicated a severe degree of aortic incompetence attributed largely to the healed bacterial endocarditis. This hazard of further aortic valve damage and increased insufficiency at the time of subacute bacterial endocarditis is now well recognized.[60, 61, 63, 64]

Mitral Valve Aneurysm. In 2 instances in the 17 postmortem cases aneurysms of the anterior leaflet of the mitral valve were found. In 1 (patient F.G.) the size of the aneurysm probably obstructed the mitral orifice until its perforation later resulted in severe mitral regurgitation and congestive failure.[65] Saphir and Leroy demonstrated 5 true aneurysms of the mitral valve in 12 hearts from patients with bacterial endocarditis seen between 1943 and 1946, but they had encountered none in a comparable series before the penicillin era.[66] The lesion occurs most frequently on the anterior mitral leaflet, especially in the presence of aortic regurgitation, and it has been found post mortem in a patient as long as 5 years after bacterial endocarditis.[67]

Valve Perforation. Eight patients had perforation of a cusp of the mitral or aortic valve not related to aneurysm formation. All but 1 showed severe progressive congestive failure leading to death. Although it is often

TABLE 5.—*Pathologic Findings in "Healed" Subacute Bacterial Endocarditis*

	Patient	Age	Sex	Type of heart disease	Interval between cure of SBE and death	Congestive heart failure	Valve lesion	Myocardium	Other
1	H.D.	47	M	rheumatic	1 mo.	yes	small aortic vegetations with bacteria*	focal interstitial fibrosis	
2	M.D.	43	F	rheumatic	2 mo.	yes	perforation aortic cusp		
3	H.Y.	46	M	rheumatic	2 mo.	yes	perforation aortic leaflet mitral valve	focal fibrosis	died with coronary embolus and infarction
4	A.F.	59	M	calcific aortic stenosis	5 mo.	yes	perforation aortic valve	large areas fibrosis	
5	A.R.	57	F	calcific aortic stenosis	6 mo.	yes	calcified nodules aortic valve perforation mitral valve sinus Valsalva aneurysm	patchy fibrosis	
6	A.S.	35	F	rheumatic	8 mo.	yes	perforation aortic cusp	fibrosis Aschoff bodies	nephritis with uremia
7	A.K.	35	M	rheumatic	9 mo.	no	perforation aortic cusp, acute endocarditis on mitral valve	focal fibrosis and abscesses	endocarditis twice; Staph. aureus on recent mitral valvulotomy site
8	G.C.	68	M	rheumatic	11 mo.	yes	small healed mitral vegetations	interstitial fibrosis	died with pulm. emboli and recent myocardial infarct
9	P.E.	32	M	rheumatic	1 yr.	no	free aortic regurgitation with marked scarring aortic valves and ring	occasional fibrotic areas	angina; died at time of Hufnagel valve insertion
10	Z.F.	65	F	rheumatic	1 yr., 10 mo.	yes	small calcified aortic vegetations		died from metastatic carcinoma ovaries
11	E.R.	58	F	rheumatic	2 yr., 1 mo.	yes	no definite residual vegetations		
12	B.O.	24	F	bicuspid aortic valve	6 yr.	yes	free aortic regurgitation perforation aortic cusp mitral valve aneurysm	patchy fibrosis	endocarditis twice; Staph. aureus perforation site aortic valve; infected thrombus in Hufnagel valve
13	T.C.	23	M	rheumatic	7 yr.	no	free aortic regurgitation with scarring aortic valves	small areas of fibrosis	died 1 month after Hufnagel valve, ? arrhythmia
14	W.H.	41	M	rheumatic	8 yr., 8 mo.	yes	no definite residual vegetations		
15	L.R.	30	M	rheumatic	9 yr.	no	free aortic regurgitation with severely scarred aortic cusps		died suddenly—no evidence prior rheumatic heart disease
16	S.H.	80	M	rheumatic	10 yr.	yes	shortening post. mitral valve cusp	fibrous scars	
17	F.G.	36	M	rheumatic	10 yr., 1 mo.	yes	mitral aneurysm with perforation		

*Gram-positive organisms were found post mortem microscopically in healing vegetations, indicating probable incomplete cure.

TABLE 6.—*Recurrence of Bacterial Endocarditis*

Case	Age	Sex	Interval between attacks of endocarditis	Type of heart disease	Organism		Living duration of follow-up	Dead duration of follow-up*
					1st attack	2nd attack		
A.K.	35	M	6 mo.	RHD - AR, MS	a-strep.	Staph. aureus		Died in hospital. At p.m. healed S.B.E. aortic and mitral vales, A.B.E. mitral valve
D.D.	33	M	1 yr.	RHD - AS, AR	a-strep.	a-strep.	1 yr., 1 mo.	
P.C.	61	M	1 yr., 2 mo.	RHD - MR	a-strep.	a-strep.		7 mo. (no autopsy)
M.C.	27	F	4 yr., 5 mo.	RHD - MR, AR	a-strep.	a-strep.	4 yr., 9 mo.	
S.S.	25	M	4 yr., 8 mo.	RHD - AS, AR	Staph. albus	a-strep.		
B.O.	18	F	6 yr.	Bicuspid aortic valve	?	Staph. aureus		Died in hospital. Healed S.B.E. mitral valve with perforation and A.B.E. aortic valve
E.D.	25	F	6 yr., 6 mo.	PDA - bicuspid aortic valve	a-strep.	B-strep.	4 yr., 1 mo.	
L.R.	59	F	6 yr., 7 mo.	RHD - MR	a-strep.	a-strep.		2 yr., 9 mo. (no autopsy)
F.C.	16	M	7 yr., 8 mo.	RHD - MR, AR, MS	a-strep.	Staph. albus	3 yr., 1 mo.	
L.K.	37	F	10 yr., 7 mo.	RHD - MR	Enterococcus	a-strep.	10 mo.	

*Follow-ups are from the time of the second attack.

RHD, rheumatic heart disease; PDA, patent ductus arteriosus; MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; A.B.E., acute bacterial endocarditis; S.B.E., subacute bacterial endocarditis.

difficult to determine the time of rupture, in 4 patients failure appeared shortly before death and months after cure of the infection. As with ruptured mitral valve aneurysms, the abrupt appearance of a new and loud murmur followed by otherwise unexplained heart failure may signal this event (fig. 2).

Valve Distortion. In 2 cases the pathologist suspected that unusually severe distortion of the valve had been caused by the endocarditis. In the first instance there was extensive scarring and shortening of the posterior leaflet of the mitral valve leading to mitral incompetence of high degree, and in the other case there were extensive calcium deposits on the aortic valve, the character and distribution of which probably indicated the site of the healed endocarditis.

Myocarditis. The most frequent finding in the myocardium post mortem was widespread focal fibrosis, which probably represented healed myocardial involvement secondary to bacterial endocarditis. Aschoff bodies were found in the routine sections only once. Saphir and others have emphasized the importance of the varied myocardial lesions encountered in bacterial endocarditis, which include focal and diffuse myocarditis, microabscesses, perivascular cellular infiltration, and multiple minute areas of infarction.[68-70]

Late Embolism. There were 9 instances of embolism following cure of endocarditis, but in only 1 patient was death clearly attributed to the embolus. This patient (H.Y., table 5) died 2 months after hospital discharge following the sudden onset of a coronary embolus and acute myocardial infarction.[71] Although neither late cerebral embolism nor ruptured systemic aneurysm was found in the postmortem cases, either condition may occur

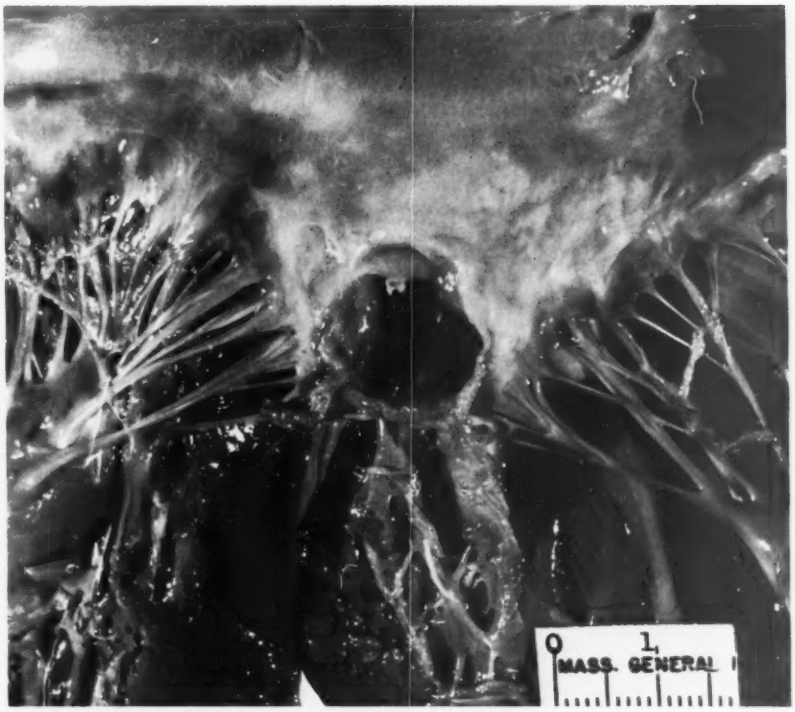

FIG. 2. Perforation of anterior leaflet of the mitral valve by subacute bacterial endocarditis. The infection was arrested by antibiotics, but the patient succumbed 4 months later with intractable congestive failure. (Case Records of the Massachusetts General Hospital, no. 43321, New England J. Med. 257: 279, 1957.)

despite successful eradication of the infection. In the living patients an iliac mycotic aneurysm was found in 1 patient 9 months after discharge and was successfully excised, and an aneurysm, possibly mycotic, was found beyond the site of aortic coaretation at operation 2 years after bacterial endocarditis. Likewise, in Cates' and Christie's series late embolism occurred up to 70 days after treatment in 15 patients who were bacteriologically cured, and a mycotic cerebral aneurysm ruptured in 7 cases from 1 to 22 months after therapy; in 2 other cases a peripheral aneurysm developed after successful therapy.

Chronic Renal Damage. Although uremia was more frequently noted prior to the antibiotic era (in 14 per cent of Bell's 108 cases),[30] only 5 patients on long-term follow-up have evidence of permanent renal insufficiency. In 2 of these 5 patients there was evidence of glomerulonephritis at postmortem examination, in one without clinical impairment (patient L.R.) and in the other with a history of progressive uremia with the serum protein nitrogen rising to 150 mg. per cent (patient A.S.). This strikingly lower incidence since the introduction of antibiotics has been emphasized by others as well.

SUMMARY

Since the introduction of penicillin therapy for bacterial endocarditis in 1944 there have been 228 patients with this disease at the Massachusetts General Hospital. In 53 instances it was of the acute form, and in 175 it was subacute. The immediate outcome and the ultimate fate of these patients have been studied.

Acute bacterial endocarditis remains an ominous and often fatal disease. In only 21

patients was the presence of an acute bacterial infection on the heart valve recognized before death; 8 of these survived. Even when the disease was recognized clinically, death often ensued before an adequate antibiotic program could be instituted.

In the subacute group 119 patients (68 per cent) recovered and 56 (32 per cent) died. Postmortem examination in 48 of the 56 revealed that the principal cause of death in one half the cases was either rupture of a mycotic aneurysm or valve cusp or an embolus to a cerebral or coronary vessel. In the postmortem group the presence of bacterial endocarditis was unsuspected in 25. Therefore the "cure rate" in those actually treated was 79 per cent.

Of the 119 patients who recovered, 60 patients have been followed for 5 years with a 69 per cent survival rate, and 23 for 10 years with 49 per cent survival. Only 1 patient has been "lost." The principal cause of death in the years after cure of bacterial endocarditis has been congestive failure.

In the 119 original survivors, 16 had a high degree of aortic regurgitation, clearly augmented by their disease in 8 instances and necessitating a Hufnagel valve in 5. Embolic episodes unrelated to active infection occurred later in 9 patients, and arterial aneurysms were found at a later date in 2. A recurrence of bacterial endocarditis from 6 months to 10 years after the original infection occurred in 10 patients (8.5 per cent), 8 of whom again had *Streptococcus viridans* infection and were rescued, whereas 2 had *Staphylococcus aureus* and succumbed.

Postmortem examination was done in 17 patients with healed bacterial endocarditis who later died. In 12 of the 17 cases a severe degree of structural damage was found to be the result of the healing process. These alterations were responsible for a variety of special syndromes now recognized as peculiar to the antibiotic era. Notable in this group was aortic regurgitation of unusually high degree, frequently associated with left ventricular failure and angina pectoris. In other instances the abrupt onset of congestive failure heralded the rupture of a weakened valve cusp. Some patients were never well again, and their insidious decline and ultimate death resulted from one or more factors including valve distortion, diffuse myocardial injury, and occasionally a reactivation of rheumatic fever. Finally, in a few instances a fatal embolus occurred.

In concluding this survey of bacterial endocarditis in the antibiotic era, 3 special features remain for further study and clarification. First in importance is the prevention of rheumatic and possibly of congenital heart disease, thereby eradicating the cardiac lesions most susceptible to bacterial invasion. Second, the protection of patients with these lesions during dental and other surgical procedures is vital; although the currently recommended programs for this purpose seem adequate in the majority of instances, the optimal antibiotic dosage and the duration of administration remain to be settled. Third, the emergence in recent years of increasing numbers of organisms resistant to presently available antibiotics poses a most serious and urgent problem.

Summario in Interlingua

Depost le introduction de therapia a penicillina in endocarditis bacterial in 1944, 228 patientes con iste morbo ha essite tractate al Hospital General Massachusetts. In 53 casos le morbo esseva acute, in 175 subacute. Le resultatos immediate e le ultime fato de iste patientes ha essite studiate.

Acute endocarditis bacterial remane un morbo de mal augurio que se termina frequentemente con le morte del patiente. In solmente 21 del casos, le presentia de un acute infection bacterial del valvula cardiac esseva recognoscite ante morte. In 8 de iste 21 casos le patiente superviveva. Mesmo in le casos in que le morbo esseva recognoscite clinicamente le morte occurreva frequentemente ante que un adequate programma antibiotic potevа esser instituite.

In le gruppo del casos subacute, 119 patientes se restabliva e 56 moriva (i.e. 68 e 32 pro cento respectivemente). In 48 del 5 mortes, examines necroptic revelava que l causa principal del morte (in un medietat

del casos) esseva ruptura de un aneurysma mycotic o de un cuspide valvular o un embolo de vaso cerebral o coronari. In le gruppo de casos studiate necropticamente, 25 habeva endocarditis bacterial non previemente suspicite. Assi le proportion de curationes in casos de facto tractate esseva 79 pro cento.

Ex le gruppo de 119 patientes qui se restabliva, 60 esseva tenite sub observation durante 5 annos, con un superviventia de 69 pro cento, e 23 durante 10 annos, con un superviventia de 49 pro cento. Le causa principal de morte durante le annos post le curation de endocarditis bacterial esseva disfallimento congestive.

Inter le 119 superviventes original, 16 habeva un alte grado de regurgitation aortic, clarmente augmentate per le morbo in 8 casos e requirente un valvula de Hufnagel in 5. Episodios embolic non relationate a infectiones active esseva trovate subsequentemente in 9 patientes, aneurysmas arterial in 2. Recurrentia de endocarditis bacterial, a periodos de inter 6 menses e 10 annos post le infection original, occurreva in 10 patientes (8,5 pro cento). Octo de istes esseva inficite per *Streptococcus viridans;* illes esseva salvate. Duo habeva *Staphylococcus aureus;* illes moriva.

Examines necroptic esseva effectuate in 17 patientes con curate endocarditis bacterial qui moriva subsequentemente. In 12 del 17 un grado sever de damnification structural esseva recognoscite como resultato del processo curative. Iste alterationes esseva responsabile pro un varietate de syndromes special que es hodie considerate como peculiar al era del antibioticos. Notabile in iste gruppo esseva regurgitation aortic de grado inusualmente alte e frequentemente associate con disfallimento sinistro-ventricular e angina de pectore. In altere casos le declaration abrupte de disfallimento congestive precedeva le ruptura de un debile cuspide valvular. Plure patientes nunquam se retrovava completemente ben, e lor insidiose declino e lor ultime morte resultava ab un o plures in un series de factores que includeva distorsion valvular, diffuse lesiones myocardial, e a vices un re-activation de febre rheumatic. Finalmente, in plure casos un embolo mortal occurreva.

Pro concluder iste revista de endocarditis in le era del antibioticos, il remane 3 aspectos special que require un studio e un clarification additional. Le plus importante es le prevention de morbo cardiac rheumatic e possibilemente etiam congenite, con le objectivo de eradicar le lesiones cardiac que es le plus vulnerabile per invasiones bacterial. Secundo, le protection de patientes con iste lesiones durante interventiones dental e alteremente chirurgic es vitalmente importante. Ben que le programmas currentemente recommendate pro iste objectivo pare esser adequate in le majoritate del casos, le melior dosage de antibiotico e le duration del administration remane a fixar. Tertio, le emergentia, in recente annos, de crescente numeros de organismos resistente al nunc disponibile antibioticos pone un seriosissime e urgentissime problema.

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CLINICAL CONFERENCE

Editor: EDGAR V. ALLEN, M.D.
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The Malignant Carcinoid Syndrome

By ROLAND E. SCHNECKLOTH, M.D., IRVINE H. PAGE, M.D., AND A. C. CORCORAN, M.D.

DR. ROLAND E. SCHNECKLOTH: This conference is concerned with some of the manifestations of malignant carcinoid tumors and the associated release of excessive amounts of serotonin into the circulation. Before undertaking any discussion of the endocrine aspects of the carcinoid syndrome, we would like to hear from Dr. Page something about the history of serotonin. Its isolation in 1948 antedated recognition of the carcinoid syndrome, the two not being linked until 1953.

DR. IRVINE H. PAGE: Serotonin has had, and promises still to have, a checkered and unexpected career. In 1947, with Dr. Maurice Rapport and the late Dr. Arda Green, we endeavored to characterize the vasoconstrictor substance which for nearly a hundred years had been known to form during the clotting or defibrination of blood. As a matter of fact, we were not as much interested in this substance, as such, as in the possibility of doing away with it. Its occurrence in serum and plasma was a major artifact in the analysis of blood for the pressor and vasoconstrictor agents that we believed might be concerned in hypertension. A year later, a potent material, closely related to tryptamine, was finally crystallized from serum extracts, its structure was partially determined, and it was given the name serotonin.[1] Rapport[2] in 1949, completed its structural identification as 5-hydroxytryptamine, complexed with creatinine and sulfuric acid and, a little later, the active amine was synthesized.

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At that time, we conceived of serotonin as an agent which probably contributed to body economy only by causing constriction of blood vessels around a clot. Nowadays we are not sure that this is the case, but we do know that it has a much broader physiologic significance. Thus, for several years, Erspamer, in Italy, had studied extracts from gastrointestinal mucosa of mammals and of various invertebrates that stimulated smooth muscle and appeared to originate from the argentaffin or enterochromaffin cells. He called the active principle in these extracts "enteramine," although it had not been isolated. In 1952, Erspamer and Asero[3] showed this material to be identical with 5-hydroxytryptamine or serotonin. Subsequently, Betty Twarog and I[4] found serotonin in the brain, especially in the hypothalamus, midbrain, and, as shown by Amin, Crawford, and Gaddum,[5] the medial part of the thalamus. Since then, it has been the subject of extensive investigation in connection with functions of the central nervous system. Serotonin is present in the blood stream, bound to platelets. This binding seems to protect the circulating serotonin from monoamine oxidase by which free serotonin is rapidly destroyed. Formation of serotonin occurs in stages, first by hydroxylation of tryptophan to 5-hydroxytryptophan and then by decarboxylation of this intermediate to 5-hydroxytryptamine or serotonin. Serotonin is then subsequently broken down by amine oxidase and excreted into the urine as 5-hydroxyindoleacetic acid.

Although the precise physiologic roles of serotonin have not been definitely established it seems to play a major part in the carcinoi

syndrome. Since carcinoid tumors appear to originate from the chromaffin cells of the intestinal tract, Lembeck,[6] in 1953, extracted one of these and succeeded in finding large amounts of serotonin. By analogy with pheochromocytomas, carcinoid tumors seem to induce significant systemic disturbances only when there are extensive metastases, usually to the liver. The appendiceal carcinoid tumors tend to be localized, while the extra-appendiceal tumors are more often invasive, not only to the regional lymph nodes, but also to distant organs. A case of metastatic carcinoid with unusual clinical manifestations, including pulmonic stenosis was reported in 1952 by Biorck, Axen, and Thorson.[7] But the first suggestion that there might be a definite syndrome associated with malignant carcinoid tumors was made by Isler and Hedinger[8] in 1953. This suggestion was confirmed and the syndrome was related to the release of serotonin from the tumor in a further report by Thorson, Biorck, Bjorkman, and Waldenstrom in 1954.[9]

These reports aroused a great deal of interest. The condition, although rare, is now well recognized. The syndrome is manifested by attacks of vasomotor disturbance, notably a peculiar transient red or violaceous flushing of the skin, by intestinal hypermotility, and in some by respiratory distress. Several cases have been complicated by endocardial fibrosis with pulmonary valvular deformity. Those who show the syndrome also demonstrate increased amounts of serotonin in the blood and increased output of the serotonin metabolite, 5-hydroxyindoleacetic acid, in the urine.

DR. SCHNECKLOTH: We would now like to present a patient who exhibits some of the features of the carcinoid syndrome. In reviewing this case, it is important to remember that not every patient with a malignant carcinoid tumor shows all features of the syndrome; this patient, for example, showed no clinical evidence of cardiovascular disease and no respiratory symptoms other than some dyspnea.

CASE REPORT

Mr. W. J. C. was referred by Dr. D. E. Nolan of the Veterans Administration Hospital, Seattle, and admitted to the Cleveland Clinic Hospital for further study. The patient was 29 years of age. He had had severe chronic diarrhea and paroxysmal attacks of flushing of the skin for approximately 4 years. In 1955, laparotomy revealed an inoperable pyloric mass with extension to regional lymph nodes; biopsy of nodules in the liver showed malignant carcinoid.

On physical examination, there was a persistent cyanotic facial discoloration without telangiectases, such as have occurred in some patients. This discoloration became even more striking during attacks of intense purple-red flushing of the face, neck, and extremities. Episodes of flushing occurred 10 to 20 times a day, lasted several minutes, and were accompanied by palpitations, nausea, abdominal cramps, and sensations of facial warmth and tingling of the skin. Tachycardia, tachypnea, and sweating were common during these attacks. Flushes usually occurred spontaneously but could be provoked by emotional stress, physical exertion, and evacuation of the bowels, and could be aggravated by standing, but they were not induced by eating or by drinking whiskey. His average blood pressure was 112/72 mm. Hg lying and 100/70 mm. Hg standing. The heart was normal. The liver was enlarged, firm, nodular, and not tender. The daily urinary excretion of 5-hydroxyindoleacetic acid averaged 239 mg. (normal range, 2 to 9 mg. per 24 hours). Arterial serum serotonin was 0.7 to 1.0 μg. per ml.

DR. PAGE: I know that both you, Dr. Schneckloth, and Dr. Dustan personally received infusions of serotonin and that you have observed the effects of such infusions in patients. Do your observations lead you to believe that the manifestations of the syndrome are due to excessive amounts of circulating serotonin such as occur during serotonin infusion?

DR. SCHNECKLOTH: That is difficult to answer. It is true that the levels of blood serotonin and urinary serotonin end-products in patients with carcinoid may show no close association with the severity of the clinical symptoms. There is also a large difference between the physiologic effects of hyperserotonemia, which has been present for months and years, and the effects of serotonin infused in tolerated doses over a few hours at most in normal subjects. We know that patients with pheochromocytomas seem to tolerate concentrations of circulating catechol amines, which would be fatal in one not adapted to their

presence. Similarly, it seems likely that patients with the carcinoid syndrome circulate amounts of serotonin which a normal subject would not tolerate. Hence, it may be impossible to make direct comparisons between the syndrome and the effects of serotonin infusions. Still, the evidence at hand supports the view that the manifestations of the syndrome in most patients are primarily attributable to hyperserotonemia. For example, massive quantities of serotonin are present in the tumors, and flushes and other aspects of the syndrome have been precipitated in some patients by palpation of the tumor. Increased amounts of 5-hydroxyindoleacetic acid appear in the urine during periods of severe flushing. Moreover, the rapid intravenous injection of large doses (2 to 4 mg.) of serotonin in normal, as well as in carcinoid subjects, will usually induce moderate, at times intense, flushes accompanied by increased intestinal motility and bladder spasm. These changes, although less intense, resemble those occurring during spontaneous attacks observed in patients with carcinoid.[10]

DR. PAGE: I am inclined to agree with you that many, if not all, of the curious effects seen in the syndrome are due to elaboration of serotonin. There are important species differences in responses to injections of serotonin. For example, in one species, the rat, large doses of the drug cause a cyanotic flush of the ears, nostrils, and paws that is similar to the carcinoid flush. Furthermore, in this regard, an injection of serotonin into rats causes brief initial hyperpnea followed by apnea and succeeded sometimes by tachypnea.[11] This initial respiratory stimulation would seem to depend on stimulation of the carotid artery and, probably, aortic chemoreceptors. Such stimulation may be the basis for the vaguely described respiratory symptoms—tachypnea, cough, wheezing, and asthma-like states noted in the syndrome.

DR. SCHNECKLOTH: The patient presented today exhibits marked tachypnea at the onset of every severe paroxysm of flushing. We have observed pronounced respiratory stimulation when large doses of serotonin are injected rapidly into normal subjects.

DR. PAGE: This patient showed no clinical evidence of cardiac disease and cardiac catheterization also indicated no significant valvular lesion. Actually, none of the 6 patients we have seen with this syndrome has shown evidences of damage to the heart. What do you suppose is the mechanism of cardiac involvement when it occurs?

DR. SCHNECKLOTH: Half, or even less than half, of reported cases had no evident cardiac lesions. Hence it is not surprising that our small group of patients showed no signs of heart disease. Pulmonic stenosis is the most common finding, with sclerotic thickening of the cusps, often with fusion of the commissures. The tricuspid valve may be affected as well, with development of stenosis or insufficiency. Endocardial fibrosis of the right atrium has also been reported, and there may be some degree of right ventricular hypertrophy. The process is apparently restricted to the right side of the heart, except in the presence of a patent foramen ovale when the mitral and aortic valves may be affected. One might conceivably confuse the cardiac symptoms with those of cyanotic right-sided congenital lesions or of chronic pulmonary disease with polycythemia. The differential diagnosis is facilitated by the fact that carcinoid heart lesions usually develop late in the course of the disease when other manifestations of the syndrome are present and recognizable.

The lesions constitute a unique form of heart disease and consist of subendothelial accumulations of fibrous tissue, rich in mast cells and free of elastic fibers.[12] One can only speculate as to their pathogenesis, since they have not been reproduced experimentally. Two possible mechanisms have been suggested. The one is hemodynamic and is based on the fact that serotonin is a potent pulmonary vasoconstrictor that considerably increases pulmonary vascular resistance and pulmonary artery pressure when injected into dogs or man. Bouts of pulmonary hypertension during flushing attacks might place repeated sudden strains on the right heart and thus account for subendocardial fibrosis limited to the right side of the heart. This explanation seems inadequate because, if it were

valid, then similar lesions should be found in people with primary pulmonary hypertension, and this is not true. A second possibility is that serotonin, as such, has a direct proliferative action on fibrosis tissue. A substantial quantity of free circulating serotonin present in mixed venous blood is probably destroyed as it perfuses the lungs; indeed, pulmonary perfusion of defibrinated blood is one of the classical technics used to rid it of vasoconstrictor material. Hence, the right side of the heart would be exposed to a relatively high concentration of serotonin, whereas the left would be spared. This chemical explanation of the fibroplasia would also be consistent with the occurrence of fibrous lesions in the left atrium in cases presenting a patent foramen ovale and with a case that has been reported in which there were pulmonary metastases and minimal aortic and mitral fibrous lesions. The hemodynamic concept would not account for either of these situations. However, an appreciable difference between serotonin levels in mixed venous and arterial blood has not been consistently found. The only positive evidence that would support this second concept is the fact that repeated subcutaneous injections of serotonin cause a noninflammatory dermal fibrosis in rats, although even with heroic doses the cardiac lesions have not been reproduced. Also prolonged administration of 5-hydroxytryptophan in rats has been unsuccessful in reproducing lesions in the heart.

DR. PAGE: I note that this patient was normotensive when supine and had a slight degree of hypotension when standing. I make a point of this because many physicians conceive of serotonin as a potent vasopressor agent and consider hypertension a part of the carcinoid syndrome. Actually, hypertension is infrequent and probably coincidental when it occurs. This is not surprising, since there are marked species and individual variations in the blood pressure responses to serotonin. In man, single intravenous injections of serotonin may have a pressor, depressor, or biphasic effect on arterial pressure and infusions of serotonin have no noteworthy effect.

DR. SCHNECKLOTH: Slight to marked falls in blood pressure are often associated with the flushing attack and even syncope may occur. In this patient, lowering the arterial pressure by tetraethylammonium chloride or sodium nitroprusside was invariably followed by attacks of flushing. Further, his pressure fell on standing and, standing, particularly during a flush, appeared to intensify the flush. This sequence suggests that hypotension, either directly or indirectly, stimulates the tumor to liberate increased amounts of serotonin into the blood.

DR. PAGE: Are there noteworthy extracardiac vascular changes associated with serotonin or with the carcinoid syndrome?

DR. A. C. CORCORAN: The effect on renal function has been an area of major concern among experimentalists. Some believe that serotonin is a very potent antidiuretic agent. We were only able to demonstrate an antidiuretic effect with comparatively large doses in rats. During osmotic diuresis in both rats and dogs,[13, 14] there seemed to be no direct effect of this agent on the mechanism of water reabsorption. In sufficient dosage in rats serotonin causes a definite antidiuresis dependent on a decrease in glomerular filtration rate. Still larger doses evoke an intense and persistent renal vasoconstriction with oliguria or anuria and focal cortical necrosis. Others,[15] using very large amounts of serotonin found that it caused diffuse renal cortical necrosis. Hence, the renal function of this patient would be of interest. Further, is anything known about the presence of renal lesions in patients with the carcinoid syndrome?

DR. SCHNECKLOTH: Curiously, no particular point has been made in published reports as to either the renal function or the possibility of renal lesions in such patients. Some patients have noted consistent decreases in urinary volume in association with flushing attacks and one of our patients whose major symptoms were intestinal, with repeated bouts of obstruction, showed oliguria during these attacks. The patient we have now under discussion has a renal plasma flow of only 198 ml. per minute (normal about 700 ml. per minute) and a glomerular filtration of 67 ml. per minute (normal 120). Another of our

patients, with much less severe disease, also showed decreased renal function with a renal plasma flow of about half normal. A slight decrease in renal plasma flow has been observed in normal subjects given serotonin in sufficient dosage. Hence, it seems reasonable to attribute the depression of renal function in these 2 patients to their hyperserotonemia. The renal ischemia present in these patients was not associated with hypertension, proteinuria, abnormal urinary sediment, or defective concentrating power.

DR. CORCORAN: The fact that renal cortical necrosis has never been observed in these patients may be attributed to their presumed tolerance to the effects of high concentrations of circulating serotonin and, since it has only been elicited in rodents, it may represent some difference in species susceptibility to this lesion. Still, it is curious that, as far as I know, no lesions have been found in the kidneys of patients dying of this disease. In our rats, we found that we could inhibit or even reverse the disturbance of renal function caused by infused serotonin by giving sufficient doses of a serotonin antagonist, bromo-lysergic acid diethylamide (bromo-LSD). However, by giving still larger doses of serotonin, the renal vasoconstriction became irreversible and was associated with focal cortical necrosis. Neither of the 2 patients whose renal functions were studied showed any increase in renal plasma flow when given this antagonist in tolerated dosage. Either, like the rats, the vasoconstriction was irreversible, or, as seems more likely from the absence of other evidences of renal disease, there was actual loss of renal tissue and, I should suppose, focal necrosis and scarring. The other clinical situation in which serotonin has been implicated in a renal disease is in the renal cortical necrosis associated with abruptio placentae, in which an assumed hyperserotonemia is associated with shock and hypotension.

DR. PAGE: The metabolic conversion to serotonin is normally a minor pathway in the degradation of tryptophan. Is there any disturbance of tryptophan metabolism in the carcinoid syndrome?

DR. SCHNECKLOTH: Sjoerdsma and others,[16, 17] at the National Heart Institute, have shown that normally only 1 per cent of ingested tryptophan is converted to urinary 5-hydroxyindoles, including serotonin and its metabolites. Functioning carcinoid tumors, possibly by reason of their having high concentrations of amino acid decarboxylase and low concentrations of amine oxidase, are equipped for rapid, steady production of serotonin. This production is almost independent of tryptophan feeding. It can use up as much as 60 per cent of available circulating tryptophan, on which the tumor evidently has a high priority. This avidity of the tumor for tryptophan is met only at the expense of other tryptophan requirements for protein synthesis and formation of nicotinic acid. Patients with the syndrome who have low protein intakes may be expected to show evidences of protein deficiency; pellagra-like symptoms have been reported. The possibility of deficiency is chemically confirmed by the fact that some patients have been shown to have low concentrations of fasting plasma tryptophan and of urinary N′-methyl-nicotinamide. None of our patients has exhibited signs of nicotinic acid deficiency. This we attribute to the fact that the supply of tryptophan in the average American diet is 5 to 10 times the minimal daily requirements. However, patients with advanced disease and chronic diarrhea may well have inadequate net protein assimilation and thus go into a state of tryptophan and nicotinic acid deficiency.

DR. PAGE: You mentioned this patient's urinary output of 5-hydroxyindaleacetic acid as averaging some 200 mg. daily. What is the significance of this determination?

DR. SCHNECKLOTH: It represents an output of more than 20 times the normal. This ranges from 2 to 9 mg. Such an increase is biochemical evidence of extensive, functioning tumor masses with a high rate of serotonin production. A survey of numerous disease states has revealed none other than the carcinoid syndrome in which there occur large increases in the excretion of 5-hydroxyindoleacetic acid.

Increased outputs have been described as a sequel to feeding bananas and slight increases have been reported in urines of patients with cancers of the larynx and trachea. The test seems therefore pathognomonic for functioning carcinoid. Since the quantitative assay is somewhat tedious, simple screening tests have been described which are reliable in cases whose rates of excretion are of the order of 40 mg. daily. We have seen 1 asymptomatic patient with liver metastases in which the screening test was negative, but quantitative measurements showed consistent, small increases in output, which ranged from 12 to 14 mg. daily.

It seems likely that some carcinoid tumors liberate indoles other than serotonin, since the urine of some patients contained large quantities of 5-hydroxytryptophan. Interestingly, some of these individuals had, in addition, large increases in blood and urine histamine presumably due to the histamine-releasing effect of serotonin. Further, the flush in some of these cases lacked the usual cyanotic hue, was more typical of a histamine flush, and seemed benefited by antihistaminic drugs.

Dr. Page: What is the prognosis of carcinoid tumors and how can they be treated?

Dr. Schneckloth: The immediate prognosis of the patient, even in the presence of a metastatic, inoperable carcinoid tumor, is not necessarily bad. Carcinoids grow slowly and there are reports of patients living 20 years after the recognition of metastases. To the extent that the occurrence of the syndrome implies widespread metastases, it is a late manifestation of the disease and death might soon be anticipated. Actually, patients have survived for prolonged periods of time, disabled only by their attacks of flushing and diarrhea.

Unfortunately, there has been little to offer these people in the way of therapy. A diet rich in protein and niacin is probably helpful. Radiation is ineffective. Surgical excision of the primary tumor and of accessible metastases is probably advisable in patients who do not exhibit the syndrome. In patients with functioning tumors and extensive metastases, there may be a distinct hazard involved in surgery. Sudden death at the time of operation has been reported and can be attributed to forceful release of lethal amounts of serotonin during excessive manipulation of tumor tissue.

Dr. Page: There has been a great deal of investigation in the past few years of chemical substances that act as serotonin antagonists. Some of these substances are competitive antimetabolites. These combine with serotonin receptor sites by virtue of their structural resemblance to serotonin, thus preventing serotonin itself from acting. Other antagonists have no structural relationship to serotonin and may act more directly in blocking one or more actions of serotonin. It was hoped that some of these might relieve the disabling symptoms of the carcinoid syndrome in inoperable patients.

Dr. Schneckloth: Our experience has been disappointing. A number of substances, such as BAS, a benzyl analog of serotonin, and bromo-lysergic acid diethylamide, although potent antagonists in vitro, were completely ineffective in the treatment of patients. Chlorpromazine seems to be partially effective in controlling symptoms. It does not affect 5-hydroxyindoleacetic acid excretion but often relieves flushes and abdominal discomfort. It is quite likely that other more potent serotonin antagonists will become available for therapeutic trial in the future. Theoretically, a substance that would specifically inhibit serotonin production by the tumor itself might be more effective therapeutically than blocking the effects of serotonin in the peripheral tissues. Such an agent would have to block either tryptophan 5-hydroxylation or the highly specific 5-hydroxytryptophan decarboxylase.

Dr. Corcoran: In view of the probable large significance of serotonin in mental and nervous functions and its possible participation in the neuropharmacology of such agents as reserpine, lysergic acid diethylamide, and iproniazid, it is interesting that these patients show no clear-cut evidences of nervous dysfunction.

Dr. Page: That is attributable to the fact that serotonin does not easily pass the blood-

brain barrier. Hence, the hyperserotonemia of patients with the carcinoid syndrome has no significant central nervous effect, although such would be anticipated if monoamine oxidase activity were impaired, as by administration of iproniazid.

DR. SCHNECKLOTH: In summary, we have described various aspects of a syndrome, only recently recognized, in which metastatic carcinoid tumors function as endocrine tumors, liberating serotonin and, in some patients, other agents. Most of the manifestations in typical cases can be attributed to hyperserotonemia. The mechanism of the associated heart disease is not clear except as serotonin may be a sclerotogenic agent. The condition is recognized from its constellations of signs and symptoms and by screening or quantitative examinations of urine for 5-hydroxyindoleacetic acid. The course of the disease is prolonged. Chlorpromazine may give some symptomatic relief. The natural history of this disease is still not fully understood. Since the carcinoid syndrome is one of nature's bizarre and potentially very informing experiments in metabolism and pharmacology, the detailed study of each one of these patients seems more than justified.

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ABSTRACTS

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ATHEROSCLEROSIS

Bragdon, J. H.: On the Composition of Chyle Chylomicrons. J. Lab. & Clin. Med. **25**: 564 (Oct.), 1958.

The cysternae chyli of rats placed in restraining cages were cannulated in order to study the composition of chyle chylomicrons which were separated by ultra centrifugation. Analysis of lipid composition of chylomicrons showed that the feeding of cholesterol led to a 3-fold increase in the cholesterol content of the chylomicrons as compared with chyle from animals fed a similar diet without the cholesterol. Feeding of large amounts of lecithin did not raise the concentration of phospholipids, indicating that practically all of the phospholipids fed were hydrolyzed in the intestine and that their fatty acids appeared as triglycerides in the chylomicrons. Chylomicrons obtained from rats absorbing olive oil contained approximately 0.5 per cent protein, which could not be reduced by repeated washings with physiologic saline, indicating that protein was an integral part of the chylomicron. Following the feeding of radioactively labeled amino acids, the protein in the chylomicrons showed high specific activity in the first hour suggesting that at least some of the chylomicron protein was synthesized in the intestinal wall.

MAXWELL

Fredrickson, D. S., McCollester, D. L., and Ono, K.: The Role of Unesterified Fatty Acid Transport in Chylomicron Metabolism. J. Clin. Invest. **37**: 1333 (Oct.), 1958.

Extending previous studies of fatty acid metabolism, the authors determined the rates of oxidation and plasma turnover at C^{14} palmitic acid administered intravenously to dogs as either chylomicron triglyceride fatty acids (TGFA) or as albumin-bound unesterified fatty acid (UFA). Analysis of specific activity in both plasma fatty acids and expired carbon dioxide showed that palmitate oxidation proceeded at similar rates following administration as either TGFA or albumin-bound UFA. Specific activity data and derived fluxes of radioactivity in both plasma as UFA and expired air as carbon dioxide showed that all chylomicron TGFA was not retransported to blood as UFA prior to oxidation. It was inferred that approximately one half of the TGFA was directly oxidized without first appearing in the UFA fraction of plasma lipid. The authors believed that chylomicra represented a plasma vehicle for transport of fat which was directly available for oxidation. Comparison of data from animals given a high carbohydrate diet with that from dogs fasted prior to fatty acid infusion showed that carbohydrate feeding decreased both the oxidation of TGFA and the amount of UFA appearing in the blood after administration of TGFA, although the time of appearance of labeled UFA was unrelated to the previous diet.

FREEDBERG

Goldner, M. G., and Vallan, L. E.: Marked and Sustained Blood Cholesterol Lowering Effect by Medication with Niacin and Pyridoxine. Am. J. M. Sc. **236**: 341 (Sept.), 1958.

A sustained reduction of the serum cholesterol levels in a group of 53 patients with hypercholesterolemia was obtained with a combination of niacin and pyridoxine. The dose of each vitamin administered during a 10-week period was 3 Gm. daily in combination. The effect was obtained in those with familial or idiopathic hy-

percholesterolemia as well as those with diabetes and myxedema. Dietary fat restriction was not essential indicating that endogenous cholesterol metabolism was affected. A protein intake of 100 Gm. daily was provided to avoid liver damage and no alteration in liver function tests was observed. The side effect of flushing was combated with ascorbic acid, reserpine and Metrazole with some improvement, however, 15 patients refused continuation of the medication after 1 week. Nausea and vomiting were prevented by taking the tablet after meals. In 20 patients completing the 10 weeks of treatment the serum cholesterol fell from an average of 338 mg. per 100 ml. to 203 mg. per 100 ml. Upon discontinuing the drugs, the serum cholesterol values rose to pretreatment levels. The mechanism of action was not known although it was suggested that niacin has some effect upon the clearing factor of the blood and upon lipid transport.

SHUMAN

Bronte-Stewart, B.: The Effect of Dietary Fats on the Blood Lipids and Their Relation to Ischaemic Heart Disease. Brit. M. Bull. **14**: 243 (Sept.), 1958.

Currently, dietary fat is commonly implicated in the production of ischemic heart disease. The authors accepted the thesis that the level of serum cholesterol may be associated with a high intake of fat foods. However, the hypothesis that ischemic heart disease resulted from a disturbance in fat metabolism was founded more on assumption than fact. Other factors, such as genetics and environment, were probably equally important. Nevertheless, of all variables in our life which we can control, the dietary fat can best be related to the disease process. Much of the accumulated data that related a fat diet to ischemic heart disease by pathology, metabolic studies, and epidemiology were reviewed. The author suggested caution in literal interpretation of these data.

KRAUSE

Boyd, G. S., and Oliver, M. F.: Hormonal Control of the Circulating Lipids. Brit. M. Bull. **4**: 239 (Sept.), 1958.

The authors reviewed the possible role of the hormones on circulating lipids. They stress caution in transferring data obtained through animal experiments to those of the human. As a representative lipid, they discussed those factors that raised and lowered the level of blood cholesterol. For example, menopause, pregnancy, diabetes, myxedema, bilateral ovariectomy and androgens raised the blood cholesterol, whereas thyrotoxicosis, ACTH, cortisone, thyroxine, an estrogens lowered it. The concentration of ci culating lipids was dependent upon changes i hepatic-cholesterol biosynthesis, degradation an excretion, interchanges between the plasma an the interstitial fluid, and changes in the plasm volume. Hormones may affect the concentratio of the circulating lipids by influencing any o these parameters. At present, it was conclude that there was insufficient evidence to reach an definite conclusions concerning the mechanis of the effect of any hormone on the circulatin blood lipids.

KRAUSE

French, J. E., Morris, B., and Robinson, D. S. Removal of Lipids from the Blood Stream. Brit. M. Bull. **14**: 234 (Sept.), 1958.

Lipids are for the most part insoluble in wate and in the blood they are linked with protein as complex water-soluble molecules (lipopro teins) and as emulsion particles (chylomicrons) The 2 main classes of lipoproteins are alpha an beta lipoproteins. Chylomicrons consist chiefly of triglyceride, but they also contain a small proportion of cholesterol and phospholipid, and in the blood they are apparently stabilized by a surface layer of protein. In general, lipoproteins are removed from the blood through the capillary membranes. The permeability of the capillaries varied for the different lipid complexes. Since beta lipoprotein particles are larger than alpha, it is likely that the capillary membrane is less permeable to them. At certain sites, cells in contact with the blood, such as reticuloendothelial cells or possibly hepatic parenchymal cells may be able to take up lipids directly. When heparin was injected into the blood there was an increase in the concentration of unesterified fatty acid in the blood and this was associated with an increased rate at which chylomicrons were removed from the circulation. The latter apparently was accomplished by the production of an enzyme which hydrolyzed chylomicron lipid. This phenomenon was responsible for the "heparin-clearing" reaction. Unesterified fatty acids occurred in the blood as soluble complexes with the plasma albumin. These complexes were very readily removed from the blood through the capillary membranes.

KRAUSE

Cornforth, J. W., and Popjack, G.: Biosynthesis of Cholesterol. Brit. M. Bull. **14**: 221 (Sept.), 1958.

During recent years attention has been drawn to the association of cholesterol and polyethenoid fatty acids and to the possible connection of these esters to the pathogenesis of atherosclero-

is. With the advent of radio-isotope technics, acetate has been shown to be a precursor of cholesterol. Furthermore, more recently data have demonstrated that at least 2 substances are concerned in the intermediate phase between acetate and cholesterol, namely: squalene and mevalonic acid. Exactly how mevalonate is synthesized from acetate and how squalene is synthesized from mevalonate remains to be discovered and is in the process of investigation.

KRAUSE

Altschul, R., and Hoffer, A.: Effects of Salts of Nicotinic Acid on Serum Cholesterol. Brit. M. J. **2**: 713 (Sept. 20), 1958.

Nicotinic acid (niacin) in relatively large doses can reduce the serum cholesterol in man and rabbits. In rabbits it can also inhibit the production of experimental cholesterol atherosclerosis. The reports on the toxicity of nicotinic acid were contradictory. However, it was pointed out that the high acidity of the compound rather than a specific action may be responsible for the occasional disturbances, such as the gastrointestinal reactions. Tests conducted on 12 healthy young individuals showed that a buffered solution of nicotinic acid was as efficacious as the pure nicotinic acid in decreasing the serum cholesterol. Hence, when nicotinic acid is poorly tolerated, a solution of nicotinic acid buffered with sodium bicarbonate (or sodium and potassium bicarbonate) deserves to be tried.

KRAUSE

Solth, K., Kohl, R., Schettler, G., and Werthemann, A.: On the Statistics of Arteriosclerosis. Verhandlungen der Deutschen Gesellschaft für Pathologie **41**: 64, 1958.

Study of autopsy findings in 16,269 patients from Basel, Switzerland, and 5,836 patients from Marburg, Germany, showed that age was the greatest single factor in the incidence of general atherosclerosis and coronary sclerosis, which became practically 100 per cent after the age of . At the same age, this incidence was greater men than in women; the difference was greatt under 50 years. Atherosclerosis involved the ronary arteries more often in men than in men. At the same age, the incidence of atherosclerosis was greatest in patients with diabetes, pertension and gallbladder disease; smallest in se with malignancies, tuberculosis, and leukeias. In Basel no differences were found in the idence of atherosclerosis during the war (1939-5) and after the war (1946-1953). A marked crease during the war years, which were accompanied by deficiencies in alimentary fats, was previously found in Marburg in clinical observations but this must yet be confirmed on a larger autopsy material.

LEPESCHKIN

Friedman, M., and Byers, S. O.: Source of Excess Plasma Cholesterol in Phosphatide-Induced Hypercholesterolemia. Am. J. Physiol. **195**: 185 (Oct.), 1958.

Various tissues of the rat were analyzed for their cholesterol content during phosphatide-induced hypercholesterolemia. Rats prefed a sterol-free diet showed an increase in cholesterol content of the liver and decreased cholesterol content of the adrenal gland at the peak of hypercholesterolemia. There was no change in the cholesterol content of other organs or tissues. In rats prefed excess cholesterol, a decline in liver as well as adrenal cholesterol occurred with no discernable change in other tissues. It was postulated that induced hyperphospholipidemia appears capable of mobilizing only stored or excess cholesterol from any tissue.

KAYDEN

Lewis, L. A., Page, I. H., and Kolff, W.: Serum Lipoproteins and Cholesterol Changes in Nephrectomized Dogs Maintained by Peritoneal Dialysis. Am. J. Physiol. **195**: 161 (Oct.), 1958.

Low-density lipoproteins and serum cholesterol concentrations were increased in dogs after bilateral nephrectomy maintained by peritoneal dialysis. The high-density fraction, which is the major lipoprotein fraction in the normal dogs, decreased moderately. When a high-protein diet was fed, the lipid changes were accentuated. Blood pressure rose in all nephrectomized dogs, but there was no correlation between elevation of blood pressure and changes in concentration of cholesterol and lipoproteins of the serum. Extensive arteriolar necrosis was present in many of the dogs at necropsy but this did not appear to be correlated with the changes in cholesterol and lipoproteins, except that the more marked changes occurred in high-protein-fed animals. No significant serum lipid changes were noted in starved dogs after 5 days. It was suggested that the postnephrectomy lipid pattern may be related to stimulation of adrenal activity.

KAYDEN

Caren, R., and Corbo, L.: The Degree of Unsaturation of Plasma Lipid Fractions in Coronary Artery Disease. Am. J. M. Sc. **236**: 362 (Sept.), 1958.

The degree of saturation of the fatty acids of the various plasma lipid fractions of 8 normal

subjects was compared to that of 7 patients with myocardial infarction. If a deficiency of unsaturated fatty acids predisposed to atherosclerosis, a significant difference in the iodine number of at least 1 lipid fraction should be detected. The results failed to demonstrate any significant difference in the iodine numbers of the plasma cholesterol esters, phospholipids, triglycerides, or unsaturated fatty acids in the group with coronary artery disease as compared to normal controls. This would indicate that the plasma fatty acids in respect to unsaturation were similar in the 2 groups. The theory that a deficiency of unsaturated fatty acids was of etiologic importance in atherosclerosis was not supported by this study.

SHUMAN

Uotila, U., Raekallio, J., and Ehrnbrooth, W.: Goitre and Arteriosclerosis. Lancet **2**: 171 (July 26), 1958.

Postmortem findings in 250 deaths from coronary sclerosis were compared to the findings in a group of 250 individuals of similar age and 6 who had died of natural or violent causes. The thyroid gland weighed more and the incidence of goiter was greater in the group with coronary sclerosis although no other endocrine organ was significantly different. Among these with coronary sclerosis those with goiter were heavier than those without goiter. The heart weighed more in the goitrous coronary sclerosis subjects than in the nongoitrous group. A pathogenetic relationship between goitre and arteriosclerosis through the possible role of hypothyroidism and increased thyrotropin production was postulated.

KURLAND

Roine, P., Pekraninen, M., Karvonen, M. J., and Kihlberg, J.: Diet and Cardiovascular Disease in Finland. Lancet **2**: 173 (July 26), 1958.

The epidemiology of cardiovascular disease in Finland was of special interest because the mortality rate of men from coronary disease was higher there than in any other European country. To determine whether the higher incidence in East Finland as compared to West Finland was due to diet, food consumption was determined by weighing, and the daily calories and nutrients were calculated. Thirty-five per cent of daily energy was derived from the 98.9 to 105 Gm. of daily fat which was similar in East and West, both in summer and winter. There was a higher consumption of bread, milk, butter, and fish in the East and of vegetables, margarine, and eggs in the West. More protein was consumed in the East, especially in summer. No significant statistical difference existed in the intake of saturated fatty acids or poly-enes. In both areas, the intake of saturated acids compared to poly-enes was rather large. The intake of iodine, ascorbic acid, and vitamin E was significantly larger in the West.

KURLAND

Keys, A., Karvonen, M. J., Fidanza, F.: Serum-cholesterol Studies in Finland. Lancet **2**: 175 (July 26), 1958.

The surprising incidence of coronary disease in Finland, particularly East Finland, led to a field study of total cholesterol and alpha- and beta-lipoproteins in 869 healthy men in Helsinki and in 2 rural regions. The average total cholesterol in men in the populations studied in Finland was higher than that of men studied elsewhere. The difference was due to the beta-lipoprotein fraction. At all ages and work grades, the averages were higher in East than in West Finland particularly over age 30. Environmental rather than hereditary factors seemed to be important. The cholesterol level appeared to be somewhat related to the habitual level of physical activity among men aged 40 to 44. Smokers tended to have higher cholesterol levels and lower blood pressures than nonsmokers. Women had higher levels of alpha-lipoprotein though the level of total cholesterol was similar to that for men.

KURLAND

Kallner, G.: Epidemiology of Arteriosclerosis in Israel. Lancet **1**: 1155 (May 31), 1958.

Extensive immigration to Israel has produced a population of diverse backgrounds permitting extensive epidemiologic investigation. For arteriosclerotic heart disease, there was a distinct preponderance of people of occidental over those of oriental origin, but this preponderance was absent or even reversed for vascular lesions of the nervous system. Similarly, men exceeded women in the incidence of coronary localization but not of cerebral. It is suggested, tentatively, that coronary and cerebral arteriosclerosis may be 2 basically different phenomena.

KURLAND

BLOOD COAGULATION AND THROMBOEMBOLISM

Toohey, M.: Clinical Experience with Warfarin Sodium. Brit. M. J. **2**: 892 (Oct. 11), 1958.

Warfarin was used to treat 175 patients with thromboembolic disease. It acted rapidly and 95 per cent of all patients reached therapeutic prothrombin levels in 36 hours. With daily doses of the drug adequate to maintain a therapeutic prothrombin time the duration of action wa

about 36 hours. In large doses warfarin had a sustained effect up to 5 days. The authors recommend 35 to 50 mg. for initial therapy. They found the average maintenance dose to be 9 mg., and 80 per cent of all patients were maintained on daily doses of 5 to 15 mg. Prothrombin time was rather easy to control with warfarin both for short- and long-term therapy. Care must be taken to allow for its cumulative action. Variations in daily dosage of as little as 0.5 mg. are suggested for optimum control of the anticoagulant effect.

KRAUSE

Jordan, F. L. J., and Punt, K.: The Problem of Interpretation of Results Obtained by Long-term Anticoagulant Treatment in Myocardial Infarction. Acta med. scandinav. **162**: 137, 1958.

After discussing the many difficulties involved in the evaluation of results and the choice of patients in the long-term ambulatory anticoagulant treatment of myocardial infarction, the authors urged that some standard method for the expression of data be adopted so that the results of various series would be mutually comparable. They presented a diagram and table used for this purpose which separated primary from recurrent infarction and concerned itself with recurrences, thromboembolic complications, and deaths during short- and long-term therapy in both groups. In order to make the plan applicable to varied periods of treatment, the results were recorded for each 6-month period following institution of treatment.

FREEDBERG

Hanway, J. W.: Pulmonary Thromboembolism: An Analysis of 169 Autopsied Cases. New York State J. Med. **58**: 2783 (Sept. 1), 1958.

The author reviewed 169 cases of pulmonary embolism and infarction. In 47 instances pulmonary thromboembolism was the cause of death, in 26 it was a contributory cause, and in 96 it was an incidental cause of death. In this particular series, pulmonary embolism or infarction occurred in 11.2 per cent of 1507 autopsied cases in a 6-year period. Sixty-five per cent of the patients came from the medical service and 26 per cent from the general surgical service. Evidence was presented to support the contention that this was a disease of the aged, especially the cardiac patient or those with metastatic malignant disease. In the surgical patient it was a particularly prominent problem in those who had undergone laparotomy or lower extremity amputation. Pulmonary infarction complicated embolism in about one half of the cases, and about two thirds of the infarcts were found in the lower lobes of the lungs. As in other studies, the author agreed that the source of the majority of pulmonary emboli was asymptomatic leg-vein thrombosis. When adequate study was obtained and the diagnosis of pulmonary embolism or myocardial infarction was still in doubt, it was recommended that anticoagulant therapy be used (providing no contraindication to it existed). It was conceded that an occasional patient without the disease may be treated with this regimen.

KRAUSE

Wroblewski, F., and Manso, E.: Effects of Certain Anticoagulants on Serum Enzyme Activity. J.A.M.A. **167**: 2163 (Aug. 20), 1958.

The measurement of serum enzyme activity has been increasingly employed as an adjunct for the diagnostic confirmation of myocardial infarction. Several drugs may influence such activity and among them are certain anticoagulants (including bishydroxycoumarin and ethyl biscoumacetate). When such drugs are used in patients in whom diagnostic enzyme levels are obtained, cognizance must be taken of the potential hepatic effect of the anticoagulants and the reflection of this phenomenon in alteration of serum transaminase and lactic dehydrogenase activity.

KITCHELL

McDonald, G. S., and Fullerton, H. W.: Effect of Physical Activity on Increased Coagulability of Blood after Ingestion of High-fat Meal. Lancet **2**: 600 (Sept. 20), 1958.

The hypothesis that the incidence of coronary-artery disease is inversely related to the general level of physical activity was studied by measuring the effect of activity on the increase in the recalcified-plasma-clotting (R.P.C.) time which follows ingestion of a high-fat meal. The R.P.C. time at 3½ hours after a fat breakfast was significantly shorter than the fasting value while the subjects were sedentary. This significant shortening was abolished as the result of moderate exercise. The fasting R.P.C. time was shorter, and its reduction after 85 Gm. of fat was greater in convalescent-ward patients than in sedentary students.

KURLAND

Dessau, F. I., Klein, S., Lipchuck, L., O'Grady, J., and Tsalikis, J.: Heart Lesions in Mice Caused by Treatment with Bishydroxycoumarin (Dicumarol). J. Pharmacol. & Exper. Therap. **124**: 182 (Oct.), 1958.

Myocarditis with necrosis and hemorrhage was produced in the hearts of mice by adding Di-

cumarol to either purified or pellet diets at levels of from 40 to 200 mg. per Kg. diet. Vitamin E supplements to the diet did not modify this effect of Dicumarol, but it was prevented by vitamin K, at 2 times or Menadione at 8 times the dietary level of Dicumarol.

RINZLER

Carter, S. A., McDevitt, E., Gatje, B. W., and Wright, I. S.: Analysis of Factors Affecting the Recurrence of Thromboembolism off and on Anticoagulant Therapy. Am. J. Med. **25**: 43 (July), 1958.

The records of 90 patients who were followed for at least 6 months off and 6 months on therapy were analyzed to assess the benefit of anticoagulant therapy and the clinical factors associated with its failure. Although a marked reduction in the recurrence rate of thromboembolism during anticoagulation was confirmed, a statistically significant effect was not demonstrable by the chi-square test in individual patients unless they had been treated for 2 years or exhibited a strong thrombotic tendency off therapy. Thromboembolism was more likely to occur during anticoagulant therapy in patients with marked impairment of cardiac function evidenced by congestive heart failure, atrial fibrillation, and double mitral lesions. Even in the group with heart failure, there was a marked reduction in the rate of thromboembolism during therapy. The danger of recurrent thromboembolism was highest shortly after a previous episode and diminished to a steady level after the first 6 weeks. It was therefore recommended that all patients with 1 embolic episode due to rheumatic heart disease be given at least a 6 weeks' course of anticoagulants. Since there was an increased tendency to thromboembolism within 6 weeks after stopping anticoagulants, the prothrombin level should be lowered gradually when therapy is to be discounted.

KURLAND

CONGENITAL ANOMALIES

Wood, P.: The Eisenmenger Syndrome. Brit. M. J. **2**: 701 (Sept. 20), 1958.

The author defined the Eisenmenger complex in the light of present knowledge as pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over 800 dynes sec./cm.^{5}), with reversed or bidirectional shunt through a large ventricular septal defect (1.5 to 3 cm. across). As a syndrome he widens his concept to include a shunt at any level and then lists 12 causes of the syndrome. These are patent ductus arteriosus, aortopulmonary septal defect, persistent truncus arteriosus, transposition of the great vessels (with ventricular septal defect), single ventricle, ventricular septal defect, common atrioventricular canal or persistent ostium primum, single atrium, atrial septal defect, hemianomalous pulmonary venous drainage, total anomalous pulmonary venous drainage and corrected transposition (with ventricular septal defect). As defined in his paper the incidence of the Eisenmenger syndrome was per cent of the first 1,000 cases of congenital heart disease in his series. All patients with Eisenmenger syndrome had cyanosis, clubbing, polycythemia, and effort dyspnea, usually dating from infancy or early childhood. Recurrent hemoptysis began in adult life and can prove fatal. If patients survive other risks, such as cerebral abscess, bacterial endocarditis, and ill advised surgical intervention, they succumb finally to heart failure, usually in the fourth or fifth decade. Physical signs common to all include a small or normal pulse, normal venous pressure, with or without slight dominance of the a waves, an impalpable left ventricle, and a slight or moderate lift over the right ventricle and pulmonary artery. On auscultation a loud pulmonary click followed by a short pulmonary systolic murmur, a palpable and sharply accented pulmonary component of the second heart sound, and often a loud pulmonary diastolic murmur can be heard. The characteristic venous pulse and auscultatory signs of tricuspid incompetence may complicate the picture. The electrocardiogram shows a normal or rather prominent P wave and usually moderate or considerable right ventricular preponderance. X-rays revealed conspicuous dilatation of the pulmonary artery, slight to moderate cardiac enlargement (chiefly of the right ventricle), and peripheral vascular markings that are usually oligemic, but which may be normal or even slightly plethoric.

KRAUSE

CONGESTIVE HEART FAILURE

Jaenike, J. R., and Waterhouse, C.: The Nature and Distribution of Cardiac Edema. J. Lab. & Clin. Med. **52**: 384 (Sept.), 1958.

Patients with congestive heart failure accompanied by gross peripheral edema, hepatic congestion, and venous hypertension with failure due to rheumatic, arteriosclerotic, or hypertensive heart disease were studied. All patients were on a metabolic balance ward where measurements of water, sodium, potassium, chloride, and nitrogen were performed. All patients received a low-sodium diet and digitalis, and certain of the patients received Thiomerin while the others received no additional diuretic the-

ıy. Sodium, potassium, chloride, and nitrogen ere analyzed in diet, urine, and stools; changes extracellular fluid were calculated from loride space, and in those subjects studied dy water was determined by deuterium dilu- on before and after diuresis. In all patients udied with or without additional diuretic ther- ıy, chloride space contraction approximated tal water loss, indicating an insignificant ange in the cellular water compartment dur- g diuresis. In those subjects showing spon- neous diuresis and in those who responded adily to mercurial diuretics with a loss of oss edema, the ratio of sodium to chloride ex- eded unity. However, in those patients in whom suboptimal response to diuretic therapy oc- urred and who never became entirely edema ree, chloride loss exceeded sodium loss. This latter group was clinically felt to have more severe and advanced heart disease and had pre- viously been partially or completely refractive to conventional forms of treatment. No con- sistent pattern of potassium metabolism could be established throughout the entire patient group. Nitrogen balances were also variable. No uniform cellular cation shifts could be demon- strated during diuresis. In those subjects in whom loss of cell potassium occurred, there was a reciprocal shift of sodium into the cells. In the majority of subjects the calculated decrease in total cation exceeded the observed negative balance, a finding interpreted by the authors as evidence of cation binding or osmotic inacti- vation.

MAXWELL

CORONARY ARTERY DISEASE

Gerlis, L. M.: Cutaneous Petechiae in Fatal Coronary Artery Disease. J. Clin. Path. 11: 391 (Sept.), 1958.

Seven instances are described in which cu- neous petechiae were found at necropsy in tients who had died of acute coronary insuf- iency. These petechiae were found to have curred in areas commonly associated with re- rred cardiac pain. Two of the 7 patients had en subjected to frequent clinical examinations fore death and in neither cases had cutaneous techiae been noticed. In 4 of the 7 patients ere were hemorrhages directly related to the ronary arteries themselves; in 3 of these there re hemorrhages in the coronary adventitia, d direct involvement of the nerve elements y have played some part in the production vagospastic reflexes of the skin and coronary teries. In the fourth patient there was sub- imal hemorrhage in the wall of the coronary tery.

MAXWELL

Glathe, J. P., and Achor, R. W. P.: Frequency of Cardiac Disease in Patients with Strokes. Proc. Staff Meet., Mayo Clin. 33: 417 (Aug. 20), 1958.

One hundred fifty-five patients with a primary diagnosis of central nervous system disease were analyzed. In 66 (43 per cent) of these patients the acute symptoms were ascribed to cerebrovascular disease. Of the 66 patients, 8 (12 per cent) had simultaneous acute myocardial infarction associated with their illness; 3 had concomitant acute coronary insufficiency; 4 had other concurrent cardiac disease productive of emboli to cerebral arteries; and in 4 additional patients with cerebral symptoms there was a strong likelihood of associated acute coronary insufficiency. It was rather surprising to find that of the 66 patients who had presenting symptoms of strokes, 15 (23 per cent) had associated acute cardiac disease. Hence, in all patients with the clinical picture of cerebrovascular disease, it is important to be aware that not uncommonly cardiac disease may be the mechanism primarily at fault. Prompt recognition of this situation with an accurate diagnosis will enable specific therapy to be employed and this may result in a more favorable prognosis for the patient.

KRAUSE

Glotzer, S.: Symmetrical T-Waves in Myocardial Infarction. New York State J. Med. 58: 2667 (August 15), 1958.

The T wave is normally asymmetrical with a slow rising, ascending limb, and a more rapidly descending terminal portion. The vector TsE loop showed this uneven angular velocity. Tall symmetrical T waves were often seen in the precordial leads when myocardial infarction had occurred in the posterior, lateral, or inferior walls and could also occur in infarctions of the anterior wall that extended to the lateral or diaphragmatic surfaces of the heart. Although hyperpotassemia and certain gastrointestinal diseases may produce similar electrocardiographic changes, these conditions can usually be differentiated clinically. The most acceptable reason for the production of a symmetrical T wave was a change in the direction of the vector TsE loop to a more anterior position when the posterior portion of the myocardium was injured. When ischemic S-T depression first appeared, the T wave often became symmetrical. It increased in amplitude during the healing phase, and could remain, often permanently, as the only sign after scar formation was complete. It was suggested, but not proved, that when the myocardium was injured, potassium was released into the extracellular fluid, producing the same

electrocardiographic effect as hyperpotassemia. However, the base of the "hyperpotassemic T wave" was narrow as contrasted to the broad base of the "coronary T wave."

KRAUSE

Szilagyi, D. E., McDonald, R. T., and France, L. C.: The Applicability of Angioplastic Procedures in Coronary Atherosclerosis. Ann. Surg. **148**: 447 (Sept.), 1958.

In order to determine the feasibility of applying direct surgical methods in the treatment of coronary artery disease, the coronary circulation of 190 autopsied hearts was studied after injection with a barium-glycerine mixture. Occlusive coronary lesions were found in 114 hearts. Of this group 35 patients had had no clinical manifestations. Of the 79 patients with clinical arteriosclerotic disease, 23 had had angina pectoris as their sole or main clinical manifestation. The earliest and most sharply localized occlusive lesions were found in the subclinical group and the most advanced and widespread involvement occurred in those patients with angina pectoris. Taking into consideration the topographic accessibility of the lesions, as well as the luminal size and outflow characteristics of the main coronary branches, the rate of possibility of surgical palliation was judged to be 17 per cent in the subclinical group and 43 per cent in the clinical group, whereas the possibility of surgical curability was estimated to be 40 per cent in the subclinical group and only 13 per cent in the clinical group. This study pointed out the limited role of direct surgical procedures in the treatment of coronary atherosclerosis at the present time and indicated the need for a safe, reliable method of coronary angiography in selecting those few patients who may be helped by such surgery.

SAGALL

Reimers, H. F.: Contribution to the Study of Coronary Aneurysms. Zeitsch. Kreislaufforsch. **47**: 813 (Sept.), 1958.

In a 78-year-old woman without cardiac symptoms, who died in hepatic coma, autopsy showed a fusiform aneurysm of the intermediate branch of the ramus descendens of the left coronary artery, about 20 mm. in cross section. The aneurysm was filled with a partly organized thrombus. The internal elastic lamina had practically disappeared in the wall of the aneurysm, while the media contained numerous thin-walled blood vessels resembling those found in angiomas. These findings were probably responsible for the formation of the aneurysm.

LEPESCHKIN

Malhotra, R. P.: Some Aetiological Aspects of Coronary Heart Disease. Brit. M. J. **2**: 528 (Aug. 30), 1958.

Based on a study of 867 patients seen during 1948-55, the Indian point of view on etiologic aspects of coronary heart disease was presented. Observations relative to age, profession, family history, body build, and the association with diabetes and hypertension did not differ from those of the Western world. The sex ratio, too, was much the same as that described by Western authors. Feminine immunity was no greater in India in spite of the fact that women lived a more sheltered and indoor life, that they were mostly vegetarian, and that addiction to alcohol and smoking was almost unknown to them. The fat content of the Indian diet was poor as compared with European standards. Consequently the authors doubted that dietary fats played a significant role in causing coronary heart disease. Also, it was noted that vegetarians were no less prone to develop coronary disease, and the same was true of non-smokers. One-half of the patients belonged to the Sikh community, whose religion forbids smoking. Obesity, long considered in the etiology of coronary heart disease, was particularly evident in the female patients. The authors recognized that the standard of vital statistics in India was not equal to that of the Western world. Hence, the true incidence of coronary heart disease was probably not accurately known. However, coronary artery disease was present in 867 cases or 28.4 per cent of 3,054 cardiac patients. The writers concluded that coronary disease was not uncommon in materially less favored countries such as India.

KRAUSE

Thomas, A. J., Cochrane, A. L., and Higgins, T. T. T.: The Measurement of the Prevalence of Ischaemic Heart-disease. Lancet **2**: 540 (Sept. 13), 1958.

The problems in developing technics for measuring ischemic heart disease in unselected populations and ensuring comparability of the medical indices were demonstrated in 2 surveys of ischemic heart disease made on a random sample of miners and ex-miners and, for contrast, the inhabitants of an agricultural area. The population at risk was a random sample of inhabitants enumerated by a private census. The diagnosis of ischemic heart disease was based on clinical, radiologic, and electrocardiographic evidence. The last was most valuable but suffered from technical difficulties and considerable difference of interpretation by independent cardiologists. No significant difference between the 2 areas in prevalence of ischemic heart disease was proved. Those persons diagnosed as having ischemic

heart disease were taller and heavier than the others. The siblings of men with ischemic heart disease had a higher mortality than the siblings of the controls. There was no significant difference in the mean serum cholesterol levels.

KURLAND

Gorlin, R.: Studies on the Regulation of the Coronary Circulation in Man. I. Atropine-induced Changes in Cardiac Rate. Am. J. Med. **25:** 37 (July), 1958.

The effects of atropine cardioacceleration on the coronary circulation were studied in 6 patients. Coronary flow was measured by the nitrous oxide desaturation method following catheterization of the coronary sinus. One to 1.4 mg. of intravenous atropine sulfate increased the cardiac rate and, in parallel fashion, oxygen consumption. Coronary vascular diastolic resistance decreased, and coronary flow increased in proportion to the increase in myocardial oxygen consumption. Atropinization produced virtually no other changes in hemodynamics once a steady state was reached.

KURLAND

Mihaly, J. P., and Whiteman, N. C.: Myocardial Infarction in the Negro. Historical Survey as It Relates to the Negro. Am. J. Cardiol. **2:** 464 (Oct.), 1958.

The experience with myocardial infarction at the Harlem Hospital, New York City, from 1950 through 1954 was reviewed. This diagnosis was suspected in 312 of 111,323 patient admissions and confirmatory data were available in 152 of these. One hundred thirty-one were Negro; 20 were Caucasian, the incidence ratio being 1:2 respectively. Of the Negro patients, the average age was 58 years and 52 per cent were men. Eighty-seven per cent described precordial pain accompanying the infarction, which contrasts with a number of reports claiming that the Negro was less subject to cardiac pain than the Caucasian. The case fatality rate was 47 per cent, which was probably heightened by the presence of other heart disease or diabetes mellitus in 71 per cent of the whole Negro group. The authors concluded that myocardial infarction in the Negro was similar in incidence and in clinical characteristics to that occurring in the general population.

ROGERS

Schrire, V., and Uys, C. J.: Cardiac Infarction in the Bantu. Am. J. Cardiol. **2:** 453 (Oct.), 1958.

The rarity of cardiac infarction in the Bantu and to a lesser degree in other native Africans was confirmed. Coronary atherosclerosis in the Bantu was even rarer, and adequate explanation of this was lacking. Cardiac infarction was found in 3 of 188 adult Bantu autopsied in the 1952-1956 period in 2 Capetown hospitals. The same number of cases was detected electrocardiographically during those 5 years in which there were 760 such instances in Europeans. Of the autopsied patients, 1 was a 40-year-old obese man who had angina pectoris for 3 months, then died suddenly from thrombosis of diffusely atherosclerotic coronary arteries. The other 2 patients were men aged 39 and 45 years. Both had cardiac infarcts apparently resulting from insufficiency of nonatherosclerotic coronary arteries; 1 had severe hypertensive heart disease and the other had syphilitic aortic regurgitation and heart failure but no significant coronary ostial narrowing.

ROGERS

Wollheim, E., and Schneider, K. W.: On Hemodynamics After Myocardial Infarction. Arch. Kreislaufforsch. **28:** 171 (July), 1958.

In 77 patients with acute myocardial infarction, observed within the first 24 hours, the active blood volume has been measured. The blood volume was calculated from venous hematocrit and Evans-blue dye dilution in samples obtained 4 to 9 minutes after injection. No systematic error has been found in previous independent studies comparing isotope tagging and dye-dilution methods to measure the red cell mass. Other hemodynamic data included arterial pressure, direct venous pressure, and fluoresceein or decholin circulation time; estimates of the cardiac output were obtained from the amplitude/rate product (Liljestrand-Zander) and also from simultaneous blood volume and circulation-time determinations. In 70 of these patients a decrease in active circulating blood volume was found; 58 of these had no evidence of cardiac failure; 35 had also initial hemoconcentration, indicative of shock as defined by Wollheim; 23 were in simple hypovolemia. Actual circulatory collapse, with arterial pressure below 80 mm. Hg, was uncommon in myocardial infarction. In 19 patients the venous pressure was increased, and the circulation time prolonged, indicating mechanical cardiac incompetence: the blood volume was then increased in 7 patients (with decompensation); it remained low in 12 others (without decompensation). Evidence of cardiac failure had very serious prognostic implications: mortality was 80 per cent in this series. In the treatment of circulatory failure those sympathomimetic amines were advocated that increased the circulating blood volume and had little hypertensive effect; digitalis should be used only when there is evidence of cardiac incompetence. Transfusions were less beneficial in these patients than in other patients with shock, and were potentially dangerous. In view of its effect on

active blood volume the armchair treatment was contraindicated. CALABRESI

Lenegre, J., and Himbert, J.: The Anatomic Lesions of Common Angina Pectoris Due to Coronary Atherosclerosis. Arch. Inst. de Cardiol. Mexico **28**: 273 (May-June), 1958.

In a total of 760 consecutive autopsies of cardiac subjects, coronary atherosclerosis was found in 27.9 per cent: 70 of these 212 patients had had typical angina pectoris without prolonged attacks, except the terminal event in 35 of them. Detailed macroscopic study of the heart failed to show coronary artery occlusion in only 10 cases; 1 of the 3 main branches was occluded in 22 hearts, 2 in 20, all 3 in 18. Myocardial changes, absent in 15 specimens, were relatively small in 29, and large in 26: as some hearts had more than 1 large lesion, 30 infarcts were counted in this series. The average weight in 23 cases of pure coronary atherosclerosis of this series was 533 Gm.; therefore, pure atherosclerosis may induce cardiac hypertrophy. Angina of effort, pure or associated with other types of cardiac pain, was present in 148 of the total 760 autopsies: only 19 of them (12.8 per cent) did not have significant coronary atherosclerosis. It was concluded that angina pectoris was usually due to coronary atherosclerosis; coronary occlusion was common, although not always present; myocardial infarction was frequently found at autopsy. Pathologic myocardial changes were more severe in patients with spontaneous angina than in those with pure effort angina, but no great difference was noted. More than the type and circumstances of the painful episodes, the evolution of the disease suggested the degree of the arterial changes: more severe coronary and myocardial lesions were seen in cases with rapid evolution, in those of very long duration, and especially in patients with status anginosus (defined as frequent attacks of short duration). As all of these 70 subjects died of causes independent of coronary disease, and showed similar distribution of anatomic changes as the total group, it was tentatively inferred that the present series was representative of "ambulatory" patients with common angina.

CALABRESI

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Stein, I., and Weinstein, J.: High RS-T Take Off in Patients without Myocardial Infarction. New York State J. Med. **58**: (July 1) 1958.

Considerable elevation of the RS-T segment occurs in pathologic states, such as acute myocardial infarction, acute pericarditis, and ventricular aneurysm. Persistent elevation is also seen in the right precordial leads in association with intraventricular block, especially of the left bundle-branch type, and left ventricular hypertrophy. Various investigators have placed emphasis on the specific amount of elevation for it to be significant as well as on the contour of the arc that is formed when the RS-T segment rises above the junction. The electrocardiographic sign of injury is a characteristic type of displacement of the RS-T segment. This was thought to be due to failure of the injured zone to become depolarized when the muscle was stimulated. The excitatory wave was completely blocked at the boundary which separated the uninjured from the injured region. The latter, therefore, remained polarized and was positive with respect to the uninjured segment. The authors presented 5 patients with the following electrocardiographic findings: prolongation of the QRS complex, considerable elevation of the RS-T segments on the right side of the chest, inverted or diphasic T waves over the right precordium, and no change in the pattern over a long period of observation. In none of these patients was there definite evidence of organic heart disease. One of the 5 died from a neurologic disorder and at autopsy had a normal heart. It has been suggested that this pattern may result from overlapping of ventricular activation and recovery with simultaneous recordings of potentials due to depolarization and repolarization. This was manifested by the fusion of the terminal portion of the QRS complex with the initial portion of the ST-T complex. This was apparently due to prolongation of the depolarization proved by the right bundle-branch block, although an unusually early onset of repolarization may also play a role.

KRAUSE

Phillips, R. W.: The Electrocardiogram in Cor Pulmonale Secondary to Pulmonary Emphysema: A Study of 18 Cases Proved by Autopsy. Am. Heart J. **56**: 352 (Sept.), 1958.

In 18 autopsied patients with decompensated chronic cor pulmonale secondary to pulmonary emphysema, the electrocardiograms showed evidence of P-pulmonale in 20 per cent and right ventricular hypertrophy in 38 to 72 per cent, depending on the criteria employed for that electrocardiographic diagnosis. Study of these patients also showed that in chronic cor pulmonale a pattern of evolution of the electrocardiogram developed. The first and earliest stage showed no deviation from the normal electrocardiogram with the major electromotive force being di-

rected leftward and posteriorly. The second stage consisted in the development of a rightward direction of the major electromotive force but with posterior orientation remaining. This change resulted in a rightward direction of the axis in the frontal plane and a prominence of S waves in the left precordial leads, but no prominent R waves in the right precordial leads. In the third and final stage the major electromotive force was directed anteriorly as well as rightward, producing tall R deflections over the right chest leads and rightward orientation of the axis in the frontal plane. In 4 patients with serial electrocardiograms this evolution was demonstrated. The authors pointed out that the success of various criteria proposed for the detection electrocardiographically of right ventricular hypertrophy depended directly on which stages of the evolution of cor pulmonale the criteria encompassed. No criteria could detect the right ventricular hypertrophy found at autopsy of those patients with cor pulmonale and normal electrocardiograms (30 per cent in this series of 18 patients) and criteria depending on the anterior orientation of the major electromotive force of stage 3 will detect fewer cases than those dealing with the changes of stage 2.

SAGALL

Barbato, E., Fujioka, T., Debes, A. C., Pileggi, F., Filho, C. B., de Paula e Silva, P., and Decourt, L. V.: Study of the Sequence of Ventricular Activation and the QRS Complex of the Pathologic Human Heart, Using Direct Epicardial Leads. Am. Heart J. **56**: 340 (Sept.), 1958.

Thirty-one patients with either right or left ventricular hypertrophy, submitted to pulmonary or cardiac surgery, were studied with direct epicardial electrocardiographic leads to determine the spread of ventricular activation and the morphology of the QRS complex at different points on the anterior and lateral ventricular surfaces. With slight right ventricular hypertrophy only a delay in the onset of activation in all points of the right ventricular surface was found. With severe right ventricular hypertrophy the pattern of activation spread was altered in the heart as a whole. The principal change consisted of a delay of the activation in the outflow tract of the right ventricle with resulting patterns in this region of rsR′s′, rsR′S′, rRs and qRs. With left ventricular hypertrophy a delay in the activation was found over all points of the left ventricular surface, particularly in the most basal and lateral points of the lateral surface, but the sequence of activation and the morphology of the QRS complex were not significantly altered. In left ventricular hypertrophy the electrocardiographic transition zone occupied the same points as in normal hearts, but in right ventricular hypertrophy it extended to the right ventricle's intermediate zone and occasionally to the pulmonary conus. In 1 patient with pure pulmonic stenosis an inversion in the spread of septal activation was found.

SAGALL

Wilson, M., Perez-Arzola, M., and Oppenheimer, M. J.: Mephentermine and the Arrhythmias. Am. J. Med. Sc. **236**: 300 (Sept.), 1958.

The effect of mephentermine upon cardiac arrhythmias found in 12 patients with various forms of heart disease was analyzed using a 12-lead electrocardiogram following intravenous administration of the drug. In 4 patients with atrial fibrillation and 1 with atrial tachycardia, no salutary effect on cardiac action was noted. Effective reduction in a functional atrioventricular block was produced and it was believed that supraventricular tachycardia with second-degree block represented a contraindication to the use of the drug. The frequency of premature ectopic impulse formation was decreased in 5 of 6 patients studied. Of these 5 patients, 2 sustained an increase in heart rate while 3 did not. The mechanism of action was described as a decrease in the refractory period, an increase in velocity of conduction and a positive inotropic effect. The antifibrillatory effect of mephentermine suggested that it may be of value during induction of anesthesia and during open heart surgery with therapeutic cardiac arrest and in hypothermia. The direct action of the drug upon the heart muscle in increasing the force of contraction and facilitating conduction may prove useful as adjunctive treatment in patients with chronic congestive heart failure.

SHERMAN

Starr, I.: On Reading Ballistocardiograms. Am. J. Cardiol. **2**: 404 (Oct.), 1958.

This article summarized the practical aspects of ballistocardiography and was based on a broad experience of over 20 years. Of the recording technics in use, the author favored a high frequency table from which displacement was registered simultaneously with an electrocardiogram for timing. Each instrument should be individually standardized. Artifacts arising from respiration, movement of the patient or of the building, or from resonance occurred frequently but could usually be overcome. The normal ballistocardiogram was described, emphasizing the systolic components which were the more in-

formative. The diastolic components usually were not clearly produced by shin-bar instruments, and they tended to superimpose on the systolic area in marked tachycardia. In healthy young adults, the tracing was extremely consistent in form; but in older healthy persons it was less so, probably because the older heart was weaker or occult cardiovascular disease was present in some instances. Interpretation of the abnormal tracing was to a considerable extent subjective and depended first of all on a thorough knowledge of the normal record. The structure of the I wave was regarded as an important indication of the force of cardiac contraction. In general, the more abnormal the ballistocardiogram was, the more abnormal was the heart action. Four stages of abnormality were described. The utility of the ballistocardiogram was considered to be mainly one of evaluating cardiac strength and coordination, and it was of less value in detecting cardiovascular structural defects. The overall value of the method when properly used was said to be comparable to that of a knowledge of blood pressure.

ROGERS

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Blanchard, A. J., and Mertens, G. A.: Hypersensitivity Myocarditis Occurring with Sulfamethoxypyridazine Therapy. Canad. M.A.J. **79**: 627 (Oct. 15), 1958.

Brief accounts are given of 3 elderly men who received sulfamethoxypyridazine for infections of the urinary tract and who died in 1 to 3 weeks with heart failure. Autopsy in each case disclosed extensive infiltration of eosinophilic leukocytes and histiocytes in the myocardium, particularly perivascularly, but without necrosis. Coronary atherosclerosis with myocardial fibrosis also was uniformly present. No other clinical or pathologic evidence of allergy was mentioned nor was it said whether any patient had received a sulfonamide in the past. The previous reports of similar myocarditis attributed to other sulfonamides and the absence of other likely etiologic factors led the authors to believe that the sulfamethoxypyridazine therapy produced the myocarditis.

ROGERS

Selye, H.: Experimental Production of Endomyocardial Fibrosis: Lancet **1**: 1351 (June 28), 1958.

In various species of laboratory animals, predominantly subendocardial necroses can be produced after suitable conditioning with corticoids by sodium salts and stress, and these can be prevented by oral administration of potassium or magnesium chloride. Studies were undertaken to relate this experimental situation to the endomyocardial fibrosis found widely in man. Accordingly, lesions were induced by this technic in 1 group of rats and were prevented by magnesium chloride in another. In a third group, the rats were killed 20 days after cessation of treatment. In the first group, in eight of 10 animals, thick layers of subendocardial fibrosis had developed in those areas where the necroses were most plentiful. The histological appearance of these changes bore striking resemblance to the changes found in patients who died of endomyocardial fibrosis. In rats in which cardiac necroses were prevented by the prophylactic administration of magnesium chloride the secondary fibrosis did not develop.

KURLAND

Crastnopol, P., Kroop, I. G., and Levy, G.: Management of Pericardial Effusions by Pericardiectomy. New York State J. Med. **58**: 2367 (July 15), 1958.

Pericardiectomy is useful in the management of tuberculous and chronic pericardial effusion of nonspecific etiology. The authors were concerned with the applicability of this procedure to all types of pericardial effusion. A case report of a successful operation in suppurative pericardial effusion is described. The procedure in conjunction with appropriate antibiotic therapy provided wide drainage of the infection into the pleural space where infection was more readily controlled by a dependently placed, indwelling tube. Although pericardiectomy was performed in a case of pericardial effusion due to malignant origin, the authors recognized that first, local instillation of radioactive colloidal gold or nitrogen mustard should be employed to alleviate tamponade before resorting to surgery.

KRAUSE

Parker, B. M., Andresen, D. C., Thomas, W. A., and Smith, J. R.: Effect of Intravenous Fibrinolytic Enzymes on the Vegetations of Experimental Bacterial Endocarditis. J. Lab. & Clin. Med. **52**: 588 (Oct.), 1958.

Aortic or mitral valvular injury was produced in dogs with laryngeal biopsy forceps inserted in the right carotid artery, advanced to the level of the aortic valve and used to remove tissue. Animals that had evidence of valvular disease manifest by heart murmurs but with no evidence of complicating infection were given 1 to 4 intravenous injections of a suspension of *Streptococcus mitis* on succeeding days. Development of a persistent fever of 39.5 C. or more was con-

sidered indicative of active bacterial endocarditis. Positive blood culture was obtained in all febrile animals. Streptokinase and Streptodornase were administered intravenously at 12-hour intervals for 6 injections. The dogs that received intravenous enzymes survived only 3 days longer than the infected dogs that received no intravenous enzymes. This difference was found to be statistically insignificant. Only 4 of 11 enzyme-treated animals had vegetations measuring more than 6 mm., whereas 10 of 14 untreated dogs had lesions greater than this dimension. Application of the Chi-square test failed to establish a statistically significant difference. While inflammatory responses of the valves were not significantly altered in the dogs receiving enzymes as compared to the controls, it was the authors' conclusion that reduction of the vegetation suggested that fibrin deposition was impeded in the presence of active infection.

MAXWELL

Bayer, O., Brix, J., and Meyer, R. D.: On Endocardial Fibroelastosis with Particular Reference to Intra Vitam Diagnosis. Arch. Kreislaufforsch. **28**: 217 (July), 1958.

The clinical findings and hemodynamic and angiocardiographic studies are reported in a 14-year-old boy with Marfan's syndrome; the diagnosis of endocardial fibroelastosis was advanced by exclusion of other disease processes. The pertinent literature was reviewed. Only typical cases, without evidence of degenerative and inflammatory changes, should be included; the etiology of this disorder remains obscure, although its origin during embryonal life appeared likely; the causal relationship of myocardial hypertrophy and failure was discussed.

CALABRESI

HYPERTENSION

Barratt, T. R., Tobin, J. R., Jr., and O'Connor, R. B.: Intravenous Pheltolamine for Phaeochromocytoma and "Adrenaline Shock." Brit. M. J. **2**: 771 (Sept. 27), 1958.

The management of a patient with pheochromocytoma who had an unusually wild and unpredictable fluctuation of the systemic blood pressure with periods of alarming hypertension alternating with profound shock was discussed. The use of intramuscular phentolamine ("regitine") was ineffective. However, the use of intravenous phentolamine produced dramatic improvement. This procedure of intravenous titration permitted leisurely control of the operative and postoperative periods of surgical excision of the tumor.

KRAUSE

Gyöngyössy, A., and Kelentey, B.: An Experimental Study of the Effect of Ischaemia of the Pregnant Uterus on the Blood Pressure. J. Obst. & Gynaec. Brit. Emp. **65**: 617 (Aug.), 1958.

While measuring systemic arterial blood pressure uterine ischemia was induced in gravid dogs, cats, and human beings by raising intraovular pressure with balloons in the ovular cavity. In dogs, increasing intraovular pressure for 7 to 20 minutes was accompanied by a slow increase in blood pressure which the authors found difficult to distinguish from physiologic variations in blood pressure. In cats, a biphasic blood pressure response to uterine ischemia was found with an early rapid rise of 15 to 65 mm. Hg followed by a second prolonged rise after the intrauterine pressure had been released. Tachyphylaxis to repetition of filling and evacuation of the uterus was demonstrated. In 4 human subjects, intraovular filling of the uterus increased the blood pressure by 20 to 30 mm. Hg. Injection of concentrated perfusate of the uterus of the gravid dog elicited in the cat an initial fall in blood pressure followed by a slow and then a rapid rise. A similar effect was seen following injection of perfusate of the uterus of a gravid cat to the male cat. In both groups when an antihistamine was administered with the uterine perfusate, only the pressor effect was seen. The authors concluded that at least part of the pressor effect depended on a humoral mechanism and thought that this was most likely the second gradual rise seen in the cat. They concluded from the perfusate experiments that vasoactive substances can enter the circulation from the placenta and that these must at least in part include histamine or some histamine-like substance, and possibly also an acetyl choline-like substance that may be involved in the depressor effect because of associated changes observed in intestinal peristalsis after administration of the perfusate.

MAXWELL

Harrington, M., Kincaid-Smith, P., and Milne, M. D.: Pempidine in the Treatment of Hypertension. Lancet **2**: 6 (July 5), 1958.

The properties of Pempidine, a tertiary amine and simple derivative of piperidine were investigated. Like mecamylamine, it was completely absorbed from the gut, but its elimination was delayed if there was renal failure. Its excretion was greater in acid than in alkaline urine. It was concentrated in tissues rich in nuclear material, readily crossed the blood-brain barrier and was found in high concentration in the nervous system. Following intravenous injection, a fall

in blood pressure occurred in 2 minutes and lasted from 2 to 6 hours. After an oral dose, a hypotensive effect was usually observed within an hour and lasted for 6 to 7 hours. A steady hypotensive effect was maintained on an oral 5-hour schedule. Rapid elimination permitted early attainment of a stable therapeutic dose with reasonable safety. In this respect, it was superior to mecamylamine. This characteristic also resulted in early subsidence of toxic effects which were similar to those of all ganglionic-blocking agents.

KURLAND

Mendlowitz, M., Altchek, A., and Naftchi, N.: The Work and Force of Digital Vasoconstriction in Normotensive and Hypertensive Pregnant Women. Am. J. Obst. & Gynec. **76**: 473 (Sept.), 1958.

The arterial flow and pressure in the digital circulation were measured in hypertensive and normotensive pregnant women in the third trimester. Flow was measured calorimetrically, pressure with the cuff method and with a Gartner capsule: indirect heating and ganglionic blockade were used to inhibit vasoconstriction. Calculations for the work, work index, and force of vasoconstrictions were made from the data obtained. The effect of pregnancy upon digital circulation was the same as that for any factor increasing heat production. The vasoconstrictive force was decreased as was the brachial-digital systolic pressure gradient. The latter effect may be attributed to a reduced level of brachial arterial pressure in pregnancy. In the hypertensive group an increase in neurogenic vasoconstriction was observed. This finding represented the only significant difference between the 2 groups.

SHERMAN

Mendlowitz, M., and Naftchi, N.: Work on Digital Vasoconstriction Produced by Infused Norepinephrine in Primary Hypertension. J. App. Physiol. **13**: 247 (Sept.), 1958.

After sympathetic nerve inhibition by indirect heat (cradle baker) and ganglion blockade (Pendiomide or SC 1950), the sensitivity of the digital blood vessels to infused norepinephrine was measured in 15 patients with primary hypertension and 15 normotensive patients from the work of digital vasoconstriction per milligram of norepinephrine infused per minute. Sensitivity to norepinephrine was uniformly increased in the hypertension group. This was attributed to the following: the increased response in hypertension due to hypertrophy of the smooth muscle of blood vessels; the enzyme defect in the smooth muscle of hypertensive patients which rendered the effect of infused norepinephrine more intense because it was more slowly destroyed; rates of excretion of norepinephrine; and a phenomenon of nerve-ending sensitization by the ganglion blocking drug.

RINZLER

METABOLIC EFFECTS ON CIRCULATION

Peschel, E., and Schlayer, C.: Effect of Digitalis Glycosides on the Oxygen Consumption of Heart Muscle In Vitro. J. Lab. & Clin. Med **52**: 417 (Sept.), 1958.

Slices of heart muscle obtained from adult rats were placed in oxygenated modified Ringer-glucose solution and studied by the Warburg method, using 100 per cent oxygen. The digitalis preparations were strophanthin G and desacetyllanatoside C. Because of the fluctuations in the basal respiration of heart muscle in vitro that had been observed from heart to heart but much less from slice to slice of the same heart, all studies of the digitalis effect were done with simultaneous controls on slices from the same heart. An ouabain concentration of 2.5 γ/ml. was without any effect on the heart; a concentration of 5 γ/ml. caused a slight stimulation and in the range from 10 to 50 γ/ml. a significant stimulation of the oxygen consumption was found, increasing with dosage. A dose of 100 γ/ml. did not stimulate; it had a depressing effect in half the cases. The dose maximally increasing the Q_{O2} of heart muscle had a slightly depressing effect on kidney and liver respiration and a depressing effect on the oxygen consumption of the diaphragm, increasing with the dosage of ouabain. The effects on the same organs using desacetyllanatoside C were similar qualitatively with variations dependent on dosage.

MAXWELL

Peschel, E., and Georgiade, R.: Studies on the Respiration of Heart Muscle in Vitro. J. Lab. & Clin. Med. **52**: 410 (Sept.), 1958.

Hearts from adult rats were obtained immediately after death, were placed in oxygenated modified Ringer-glucose solution, and were sliced and transferred into Warburg vessels. Kidney, liver, and spleen slices were handled in the same manner and diaphragm was also used. Oxygen consumption was calculated on the basis of the dry weight of the tissue, and wet weight was assumed as 4 times the dry weight for the heart, 5 times the dry weight for other tissues. Under optimal conditions using 100 per cent oxygen the basal respiratory rate of heart slices not exceeding 0.5 mm. in thickness was 17.4 ± 3.0. In air instead of pure oxygen, the respiration rate of heart muscle slices was 9.9 ± 1.9. Average

Q_{O_2} values for heart slices at various oxygen concentrations showed that the respiratory rate was constant between 100 and 60 per cent oxygen and decreased progressively from 50 per cent downward. When oxygen concentrations less than that found in air were used, requirements of adenate diffusion required slices of such thinness that the condition of the slices was found to be inadequate. The effects of corresponding reductions in oxygen concentrations on slices of various tissues showed that the effect of the same reduction was greater in heart muscle, kidney, and diaphragm than in liver and spleen. It was found that with decreasing oxygen concentration and decreasing Q_{O_2} the lactate concentration increased, indicating anaerobic glycolysis. In experiments using slices of variable thickness, it was shown that there was a correlation between the limiting thickness for each oxygen concentration and the point where the Q_{O_2} started to decrease. These latter 2 groups of experiments were taken to indicate that insufficient oxygen diffusion was responsible for the reduced oxygen consumption found in heart slices under the influence of reduced oxygen concentrations.

MAXWELL

Spratt, J. L., and Okita, G. T.: Protein Binding of Radioactive Digitoxin. J. Pharmacol. & Exp. Therap. **124**: 109 (Oct.), 1958.

This is a radioisotopic tracer study on the protein binding of digitoxin. Both biosynthetically labeled C^{14}-digitoxin and self-radiation labeled H^3-digitoxin were used in this study. Starch block electrophoresis was used as the method for studying drug-protein binding. Drug binding by equilibrium dialysis of salt-fractionated proteins was also used. By zone electrophoresis, digitoxin binding by serum albumin could not be shown. By salt precipitation and dialysis methods, results in the radiotracer portion agreed qualitatively but not quantitatively with other investigators. The authors found that within the therapeutic range 1 mg. of rat serum protein will bind 0.01 mg. of digitoxin.

RINZLER

Vinterscheid, L. C., Vetto, R. R., and Merendino, K. A.: Myocardial Carbohydrate Metabolism During Induced Cardiac Arrest and Post-Arrest Perfusion. Ann. Surg. **148**: 481 (Sept.), 1958.

The myocardial carbohydrate metabolism of the isolated dog heart was studied in the beating and in the arrested stage. Under the circumstances of these experiments the carbohydrate metabolism of the isolated perfused beating heart proceeded at a relatively stable rate with glucose serving as the primary substrate. The uptake of glucose or lactic acid was not correlated with the arterial oxygen concentrations. In the arrested heart the energy was found to be approximately 1/1000 to 1/2000 of that of the isolated beating heart for the same time period. This energy came primarily from residual aerobic carbohydrate metabolism that was finished within the first 10 minutes of arrest. During arrest a marked fall in the pH of the blood contained in the coronary circulation was found; but unlike the abrupt drop in aerobic metabolism, this occurred gradually being 0.14 in 10 minutes and 0.38 in 30 minutes.

SAGALL

Kleinfeld, M., Rosenthal, A., and Stein, E.: Comparative Effects of DL-Thyronine, L-Triiodothyronine and L-Thyroxine on the Isolated Perfused Frog Heart. Am. J. Physiol. **195**: 63 (Oct.), 1958.

No significant changes in cardiac output, heart rate, or electrical potential were produced by 0.2 to 0.8 mg. of thyronine. Low concentrations of thyroxine (0.2 mg.) usually produced a slight increase in heart rate with no change in cardiac output. Triiodothyronine at this dose increased both heart rate and cardiac output. At higher concentrations, (0.6 mg. and above) both the latter agents decreased the heart rate and cardiac output, and produced variable degrees of heart block, arrhythmias, and electrical alternans. Electrocardiograms showed minimal effects on the P wave; the R wave was usually decreased, the S-T segment was depressed, and the T wave became increasingly inverted. The changes caused by triiodothyronine occurred earlier and were also more pronounced than those caused by thyroxine. There were no electrocardiographic effects of thyronine. The introduction of iodine atoms into the thyronine nucleus produced compounds that had marked activity on myocardial function.

KAYDEN

PATHOLOGY

Paterson, J. C., and Mills, J.: Myocardial Mast-Cell Counts in Postmortem Material. Arch. Path. **66**: 335 (Sept.), 1958.

In 67 consecutive autopsies coronary atherosclerosis was evaluated on the basis of the following: crude morphologic grading, a measurement of the thickness of the largest plaque, determinations of the total amount of concentration of lipid and of calcium present in the inner coats of the arteries. Mast-cell counts of the myocardium were also done. The authors could find no correlation between mast-cell counts and any of the 6 parameters measured. No correlation

could be made between the mast-cell concentration and the severity of the disease in any particular age group. A correlation could be made, however, between the mast-cell concentration and the incidence of myocardial infarction or other complications of coronary atherosclerosis.

MAXWELL

Constantinides, P., Gutmann-Auersperg, N., and Hospes, D.: Acceleration of Intimal Atherogenesis through Prior Medial Injury. Arch. Path. **66**: 247 (Sept.), 1958.

Focal medial necrosis was produced in a group of rabbits on a normal diet by daily intravenous injection of epinephrine, 0.05 mg./Kg. for 10 days and thyroxine 1 mg./Kg. for the last 5 of those 10 days. Ten of 28 animals died during the course of this treatment; 9 of the remaining 18 died in a rest interval following the injections and were included in the "medial injury only" group. The 9 survivors, after a rest period of 4 days were fed diets of 1 per cent cholesterol and 5 per cent cottonseed oil for 3 weeks and then sacrificed. Nine normal, untreated rabbits were fed a similar diet for a similar period and then killed; they constituted the "lipemia only" group. Both cholesterol-fed groups developed a progressively increasing lipemia at the same rate and achieved the same plasma turbidity, total cholesterol and total lipid level at the end of the 3-week cholesterol alimentation period. Both groups given injections of epinephrine and thyroxine developed medial necrosis, with 100 per cent incidence, whereas the group given no injections had negligible amounts of spontaneous medial necrosis. Of the 2 groups that were fed cholesterol diets for 3 weeks, only those that had received prior treatment with epinephrine and thyroxine developed atherosclerosis, with 89 per cent incidence. No atherosclerosis was found in the cholesterol-fed animals that had received no prior injections. In the 2 groups receiving the cholesterol feedings, aortic cholesterol in the pre-treated group exceeded that in the untreated group by 240 per cent, and aortic wet weight was greater by 40 per cent in the pretreated group. There was no difference in aortic cholesterol and aortic wet weight between the pretreated group, which had received no cholesterol, and the cholesterol-fed group, which had received no pretreatment. In the group receiving epinephrine and thyroxine followed by cholesterol the atheroma was found to overlie patches of necrotic media that were also found to extend over the apparently normal neighboring media. There was a tendency for the central area of the intimal plaques in this combined treatment group to be lipid-poor or lipid-free. In the group receiving combined treatment, 4 of 9 animals were seen to have a few coronary atheromata; none was encountered in either of the 2 other groups.

MAXWELL

PHARMACOLOGY

Winbury, M. M.: Comparison of the Vascular Actions of 1, 1-dimethyl-4-Phenylpiperazinium and Tetramethylammonium. J. Pharmacol. & Exper. Therap. **124**: 25 (Sept.), 1958.

The vascular actions of 1, 1-dimethyl-4-phenylpiperazinium (DMPP) and tetramethylammonium (TMA) were compared in anesthetized dogs. The rate of blood flow in the femoral artery was determined with a recording rotameter. The blood pressure was recorded with a pressure transducer at the inflow tubing to the rotameter close to the arterial cannula. The blood pressure and the blood flow were recorded simultaneously on a direct-writing electronic recorder. Intravenous injection of both agents produced an initial transient fall in blood pressure followed by a more prolonged rise in pressure. Hexamethonium blocked both phases of the DMPP action but the hypotensive phase of TMA persisted; this was subsequently blocked by atropine. The hypotensive phase of both compounds was selectively blocked by atropine, whereas the hypertensive phase of both compounds was selectively blocked by Regitine. Intraarterial injection of TMA into the hind limb produced local vasodilation which was blocked by atropine but not by hexamethonium. DMPP most frequently produced local vasodilation on intraarterial injection but vasoconstriction was observed in a few animals at the start of the experiment. This later changed to vasodilatation. The dilator response to DMP was blocked or converted to a constrictor response by hexamethonium, Regitine, and Ilidar, but not by atropine. Acute denervation of the limb did not alter the response to DMPP or TMA. The results indicated that TMA can stimulate both at the autonomic ganglia and at the peripheral cholinergic effector sites (cholinomimetic action). The mechanism of the local vasodilator action of DMPP was not clear except that it was located in the periphery. It was suggested that it may involve peripheral ganglion cells, an axon reflex, or direct stimulation of the smooth muscle in the vessel walls.

RINZLER

Arora, R. B.: Antiarrhythmics. Quinidine-like Activity of Some Ataraxic Agents. J. Pharmacol. & Exper. Therap. **124**: 53 (Sept.), 1958.

The antiarrhythmic action of the tranquilizing agents, reserpine, alseroxylon, benactyzine, and meprobamate was studied and compared with that of quinidine sulfate. Alseroxylon, reserpine,

nd benactyzine possessed significant quinidine-ke activity in prolonging the refractory period f isolated rabbit atria as well as in abolishing xperimentally induced atrial fibrillation and lutter in anethetized dogs. Meprobamate was not fficacious in the atrial arrhythmias although it hared the effect of quinidine to increase atrial efractoriness. It, however, equaled quinidine in he suppression of ectopic activity produced by -stage coronary ligation in unanesthetized dogs. n this test procedure, benactyzine and alseroxy-on were stronger than quinidine, while reserpine was considerably weaker.

RINZLER

Van Arman, C. G., and Drill, V. A.: Some Cardiovascular Effects of Norethandrolene (Nilevar), Testosterone and Pregesterone. J. Pharmacol. & Exper. Therap. **124:** 59 (Sept.), 1958.

In dogs, norethandrolene was investigated for effects on atrial flutter, blood pressure, heart rate, ventricular arrhythmia, and the electrocardiogram. Progesterone and testosterone propionate were evaluated for effects on atrial flutter and blood pressure. Further, all 3 compounds were studied in the isolated rabbit heart for their effects on rate, rhythm, and strength of contraction. Norethandrolone (17-ethyl-19-nortestosterone), testosterone propionate, and progesterone all depressed the amplitude of contraction of the isolated perfused rabbit heart. Northandrolone had appreciable potency in abolishing atrial flutter in dogs. Progesterone was approximately as effective as norethandrolone in this regard. Testosterone propionate did not show such activity to the same extent as the other 2 steroids. Norethandrolone did not affect ventricular arrhythmia caused by coronary occlusion. It had negligible effects on blood pressure, heart rate, and electrocardiogram, even at very large doses.

RINZLER

Pathak, C. L.: Antagonistic Effects of Acetylcholine and Nicotine on Isolated Frog Hearts. Am. J. Physiol. **195:** 61 (Oct.), 1958.

The relationship between the actions of acetylcholine and nicotine in isolated perfused frogs' hearts was studied in normally beating hearts and in hypodynamic and spontaneously stopped hearts. Both the excitatory and inhibitory effects of acetylcholine were antagonized by nicotine. It was suggested that acetylcholine and nicotine act through the same neuronal receptors and that the antagonistic effects observed in these experiments were due to competition for these receptors.

KAYDEN

Spratt, J. L., and Okita, G. T.: Subcellular Localization of Radioactive Digitoxin. J. Pharmacol. & Exper. Therap. **124:** 115 (Oct.), 1958.

The subcellular localization of digitoxin was studied with biosynthetically labeled C^{14}-digitoxin and self-radiation labeled H^3-digitoxin to gain insight into the intracellular site of action of cardiac glycosides and the manner in which intracellular particulates interact to effect myocardial contraction. Twenty minutes after a single intravenous injection, the rat cleared its vascular system of digitoxin. Upon cell fractionation of in vivo preparations, over 90 per cent of the unchanged digitoxin present in the cell was found in the soluble supernate of rat heart, kidney, and liver cells. No marked quantitative binding was demonstrated with any of the particulate fractions. Animals for in vivo study were exsanguinated and perfused before their tissues were fractionated. No functional significance concerning the intracellular localization of digitoxin could be made.

RINZLER

Watson, W. C., Thomson, T. J., and Buchanan, J. M.: Clinical and Laboratory Studies with Chlorothiazide: An Oral Diuretic.. Lancet **1:** 1199 (June 7), 1958.

The nature and degree of diuresis obtained with chlorothiazide were studied in 26 acute experiments on 22 patients with various clinical states associated with fluid retention. Following a single oral dose of 2 Gm. of chlorothiazide, there was a considerable increase in the flow of urine, particularly in the 6 hours immediately after its administration. This was associated with increased output of sodium, chloride, bicarbonate, and potassium, in that order, with little alteration of serum electrolytes. The diuresis was chiefly of the former electrolytes but if their serum level was low, the excretion of the latter was promoted. A satisfactory diuresis may occur in the absence of corresponding electrolyte loss. In general, the best diuretic response occurred in the patient who responded well to mercurials. In patients with pulmonary heart disease the response was disappointing.

KURLAND

Maxwell, R. A., Plummer, A. J., Daniel, A. I., Schneider, F., and Povalski, H.: Concerning the Mechanisms of the Cardiovascular Actions of Hexahydro - 1 - Azepinepropionamidoxime (SU-4029). J. Pharmacol. & Exper. Therap. **124:** 127 (Oct.), 1958.

This report dealt with the mechanisms underlying the peripheral action of hexahydro-1-azepinepropionamidoxime (SU-4029). Three milli-

grams per Kg. of phentolamine hydrochloride given by vein markedly reduced the pressor response to epinephrine in 7 dogs. Subsequent intravenous administration of 180 mg. per Kg. of SU-4029 in a series of 30 to 60 mg. per Kg. doses produced a stepwise return of the pressor response to norepinephrine to control dimensions in 4 dogs and partially returned the pressor response in 3 dogs. The reversal of the epinephrine pressor response evoked by phentolamine was not affected in the 7 animals by these doses of SU-4029. The blockade of norepinephrine produced by the irreversible blocking agent Dibenamine was not negated by SU-4029. Since phentolamine and Dibenamine are generally considered to function at the same site in the adrenergic receptor substance, the indication was that SU-4029 may have an action in the substance of the alpha receptors and that it may be at the same locus as that affected by Dibenamine and phentolamine. It was further suggested by the response of a series of pressor phenylethylamines following SU-4029 pretreatment that part of the action of SU-4029 was to deform that portion of the alpha receptor system affected by adrenergic blocking agents.

RINZLER

Johnson, E. A., and Robertson, P. A.: The Stimulatory Action of Acetylcholine on Isolated Rabbit Atria. Brit. J. Cardiol. **13**: 304 (Sept.), 1958.

Acetylcholine, 1 mg. per liter, restored the rate of isolated rabbit atria (but not of ventricular fibers), depressed by quinidine 2.5 to 5 mg./L. Norepinephrine 1 to 100 mg./L. had no such effect. Quinidine-arrested atria could be restarted by acetylcholine, possibly by an action on the sodium "carrying system" (excitatory mechanism) without increasing the membrane resting potential. The usual inhibitory action of acetylcholine on the rate of beat of pacemaker cells was thought due to an increase in potassium permeability which diminished the rate of diastolic depolarization.

ROGERS

Vaughan Williams, E. M.: The Mode of Action of Quinidine on Isolated Rabbit Atria Interpreted from Intracellular Potential Records. Brit. J. Pharmacol. **13**: 276 (Sept.), 1958.

Measurements of contractions, conduction velocity, and intracellular potentials were made by photographing simultaneous oscilloscopic tracings from electrically driven isolated rabbit atria bathed in varying concentrations of quinidine sulfate. Quinidine in concentrations up to 10 mg. per liter did not affect the resting potential and either shortened or did not change the half-time for repolarization, the latter corresponding with the failure of quinidine to prolong the absolute refractory period. However, the effective refractory period was prolonged by slowing the rate of rise of the action potential. Also, the conduction velocity and height of the overshoot were reduced. Quinidine thus lowers the frequency at which atria can respond to a stimulus and therefore has an antiarrhythmic action.

ROGERS

Corne, S. J., and Edge, N. D.: Pharmacological Properties of Pempidine (1:2:2:6:6- Pentamethylpiperidine), a New Ganglionic-Blocking Compound. Brit. J. Pharmacol. **31**: 339 (Sept.), 1958.

Pempidine is a tertiary amine and therefore is chemically similar to mecamylamine but not to bis-quaternary ammonium compounds such as hexamethonium and pentolinum. Its effects on cats and mice were those of a long-acting ganglionic-blocking agent without undue toxicity. While oral doses were ordinarily effective, hypotension in the anesthetized cat was difficult to produce unless the drug was injected into the duodenum. Other actions included neuromuscular paralysis of a curare-like type when large doses of Pempidine were injected intravenously, and central effects such as tremors occurred with near toxic doses. Its weak muscarinic properties, as seen on the isolated guinea-pig ileum, might be clinically advantageous by reducing the incidence of parasympathetic side effects.

ROGERS

PHYSIOLOGY

Katz, L. N., and Feinberg, H.: The Relation of Cardiac Effort to Myocardial Oxygen Consumption and Coronary Flow. Circulation Research **6**: 656 (Sept.), **1958.**

Cardiac performance requiring oxygen determines coronary blood flow. The level of arteriovenous oxygen difference across the bed is altered by local conditions of oxygen and carbon dioxide concentrations and the presence of catecholamines. The initiating factor in the equilibrium between coronary flow and oxygen extraction by the heart cannot be decided. It is more than likely that hypercapnia and catecholamines have an effect on the basic vascular tone, probably at the level of the precapillary sphincter, that results in enhanced flow and reduced oxygen extraction.

AVIADO

Gilfoil, T. M., Schopp, R. T., Morris, G. R., and Youmans, W. B.: Mechanisms of Respiratory Inhibition Produced by Sudden Aortic Obstruction. Am. J. Physiol. **194**: 155 (July), 1958.

External constriction of the descending aorta elicited immediate inhibition of breathing in dogs under pentothal-chloralose anesthesia both before and after sino-aortic denervation. Impulses initiated by traction of a ligature on the aorta were conducted into the thoracic part of the cord. There was no indication that this mechanism was activated in experiments involving internal occlusion in the innervated animals. Internal occlusion of the descending aorta elicited inhibition of breathing in dogs under morphine sulfate-chloralose anesthesia having all neural pathways intact. The inhibition was related in large part to reflexes from the sino-aortic zones. In the majority of dogs studied, the delayed inhibition of breathing following internal occlusion of the descending aorta was greatly reduced but usually not entirely eliminated by sino-aortic denervation. Therefore, some other respiration-inhibiting mechanism was involved. That the respiratory center may be relatively insensitive to changes in blood flow under the conditions of these experiments was indicated by the fact that in individual cases sudden severe changes in blood pressure in sino-aortic denervated animals were not accompanied by changes in respiration.

WENDKOS

Kao, C. C., and Hoffman, Brian F.: Graded and Decremental Response in Heart Muscle Fibers. Am. J. Physiol. **194**: 187 (July), 1958.

Simultaneous records of the transmembrane potential from 2 points in a single cardiac fiber indicate that during the refractory period when repolarization is about half complete graded responses appear close to the site of stimulation. These responses to cathodal pulses vary in amplitude with stimulus intensity and may show spatial decrement even when an overshoot is present close to the stimulating electrode. The results obtained indicate that the transition from graded to all-or-none response does not depend solely on the restoration of membrane potential. In some experiments, stimulation was accomplished by employing 1 lumen of a double microelectrode; in others single Purkinje fibers were stimulated by action potential propagated from attached papillary muscle. Similar graded responses were elicited in both instances. The experiments employing propagating action potentials as stimuli suggest the possible occurrence of graded activity as a response mechanism in the intact heart.

WENDKOS

Holland, W. C., and Tinsley, B.: Factors Affecting the Incidence of Atrial Fibrillation. Am. J. Physiol. **193**: 235 (May), 1958.

A study of fibrillation induced in isolated rabbit atria by stimulating at high frequencies (600-1,200 cycles per minute) in the presence of acetylcholine revealed it to be dependent on the ionic composition of the medium. The effects of varying the sodium potassium and calcium ion content of the bath fluid on the incidence of fibrillation were interpreted on the basis that fibrillation only began at a time when the transmembrane flux of sodium and potassium ions exceeded a critical rate. Evidence was presented that the initiation and maintenance of fibrillation are governed by separate physiochemical processes. The onset of fibrillation resulted from a sudden transient increase in permeability of the cell membrane. This latter reaction set off other biochemical processes that maintained the phenomenon.

WENDKOS

Hilton, J. G.: Effects of Hemorrhage on Blood Pressure Responses to Epinephrine and to Histamine. Am. J. Physiol. **193**: 576 (June), 1958.

Effects of hemorrhage on blood pressure responses to epinephrine and to histamine were studied in dogs anesthetized with sodium pentobarbital. A series of graded doses of either l-epinephrine bitartrate or l-histamine diphosfate was given before and after hemorrhage, and the blood pressure effects of each dose of the administered drug were recorded. The amount of hemorrhage was determined as 10 per cent of the experimental animal's Evans-blue blood volume. Blood pressure records were analyzed in terms of minimum or maximum blood pressure attained, actual rise or fall in blood pressure and duration of primary blood pressure response before and after hemorrhage. The results showed that there was a significant change in the minimum and maximum blood pressures attained, but no significant change in the actual rise, actual fall or duration of primary response of blood pressure. The amount of change in minimum or maximum attainable blood pressure was directly related to the amount of change in blood pressure that resulted from the decrease in blood volume.

WENDKOS

Selkurt, E. E.: Mesenteric Hemodynamics During Hemorrhagic Shock in the Dog With Functional Absence of the Liver. Am. J. Physiol. **193**: 599 (June), 1958.

The sequence of hemorrhagic shock was studied in dogs with functional absence of the liver produced by ligation of vascular inflow circuits.

Establishment of a portal to jugular shunt permitted continued measurement of intestinal blood flow. It was found that this vascular bed exhibited the characteristic hyperemic response previously observed in dogs with intact livers, studied under similar condition. Other hemodynamic changes symptomatic of irreversibility were observed. It is concluded that the liver made anoxic during shock does not contribute to irreversibility, and that it is more likely that it exerts a protective role. A hypothesis is advocated that hypotension creates conditions in the intestinal bed that favor production or release of vasodepressor agents or material toxic to the cardiovascular system. In the absence or impairment of the normal protective role of the liver, these gain access into the general circulation with deleterious consequences to circulatory homeostasis.

WENDKOS

Alessi, R., Nusynowitz, M., Abildskov, J. A., and Moe, G. K.: Nonuniform Distribution of Vagal Effects on the Atrial Refractory Period. Am. J. Physiol. **194**: 406 (Aug.), 1958.

The refractory period was measured at several points on the right atrial surface in anesthetized dogs. Under control conditions with the vagi cut, the values recorded at various points varied by no more than 40 milliseconds. During stimulation of the vagus nerves, singly or together, the refractory period varied widely. At some points marked effects were observed, while at others little or no effect was apparent. Reflex excitation of the vagi, induced by increased arterial pressure, yielded similar results. It was concluded that the effects of vagal stimulation were not uniformly distributed. It follows that an early ectopic impulse generated during a period of vagal stimulation was bound to be propagated along an irregular wave front as the impulse encountered areas in varying states of excitability. The likelihood of fibrillation must be enhanced by such irregularity.

WENDKOS

Klein, R. L., and Holland, W. C.: Na^{24} and K^{42} Exchange in Atrial Fibrillation. Am. J. Physiol. **193**: 239 (May), 1958.

Changes in transmembrane flux of Na^{24} and K^{42} during acetylcholine (ACh) induced fibrillation were investigated. At a mean atrial rate of 160 per minute, the efflux of potassium was estimated to be 3-45 pmole/cm.^{2}/sec. With the onset of fibrillation the efflux reached a mean value of 9.37 pmole/cm.^{2}/sec. This rate was 50 per cent greater than the combined effects of ACh (8.0×10^{-4} Gm./ml.) and stimulation (1,200 per minute) alone. With the onset of fibrillation a momentary increase of influx followed by a decrease to 1/20-1/40 the control was observed. ACh alone produced comparable effects. The rate of sodium influx was increased 10 to 15 times by both ACh and fibrillation. Similar changes in sodium efflux were noted but of a smaller magnitude. The change in fluxes noted was transient in nature with the rate returning rapidly to that of the control even though fibrillation continued. Upon cessation of the arrhythmia a momentary increase of potassium efflux was again observed. It is concluded that ACh and fibrillation increase the transmembrane flux of sodium and potassium. With the present method the onset of fibrillation is best correlated with an increase of potassium efflux above a critical rate. Since these changes are transient, it appears that the initiation and maintenance of the arrhythmia are governed by separate physiochemical processes.

WENDKOS

Gilbert, R. P., Hinshaw, L. B., Kuida, K., and Visscher, M. B.: Effects of Histamine, 5 Hydroxytryptamine and Epinephrine on Pulmonary Hemodynamics With Particular Reference to Arterial and Venous Segment Resistances. Am. J. Physiol. **194**: 165 (July), 1958.

Studies were made of the effects of histamine and 5 hydroxytryptamine ($_5$HT) on arterial and venous segmental resistance in the isolated perfused dog lung. The lung was perfused at constant flow while pressures were measured in the pulmonary artery, left atrium and in either the pulmonary artery wedge position or a small pulmonary vein. Arterial resistance changes were inferred from changes in the pulmonary artery-pulmonary artery wedge position, pressure drop, and venous resistance from the pulmonary artery wedge position-pulmonary vein pressure gradient. Changes in lung weight were recorded continuously. It was found that histamine usually caused a greater increase of the venous resistance than of the arterial resistance, while $_5$HT usually increased the arterial resistance more than the venous resistance. When the predominant resistance increase was arterial, the lung weight fell, but when there was a sizable increase of the venous resistance, the lung weight rose, presumably as a result of increased capillary blood content. The correlation coefficient between the change in lung weight and the change in venous resistance was +.791. Small pulmonary vein pressure rose after administration of epinephrine, norepinephrine, histamine, and $_5$HT. This result gives further proof of the constriction of pulmonary veins by these agents.

WENDKOS

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Blackmore, W. P.: Effect of Serotonin on Renal Hemodynamics and Sodium Excretion in the Dog. Am. J. Physiol. **193**: 639 (June), 1958.

The effects of constant intravenous infusions of serotonin with doses of 5 to 10 μg. per Kg. per minute on glomerular filtration rate, effective renal plasma flow, urinary flow, and sodium excretion were studied in trained, unanesthetized female dogs. A small but significant decrease in glomerular filtration rate associated with increased renal plasma flow occurred at the 5 μg./Kg./min. dose, indicating a specific effect of serotonin on the kidney. Similar changes were noted with 10 μg./Kg./min. dose plus a marked antidiuretic effect that occurred in the absence of any significant change in mean arterial blood pressure and an intact neurohypophysis, indicating a direct action on water reabsorption in the kidney. Urinary sodium excretion decreased with both doses as a result of a decline in glomerular filtration rate associated with increased tubular reabsorption. These results indicate that serotonin has a specific effect on the kidney and suggest that this substance may alter the caliber of the glomerular vessels to decrease renal vascular resistance.

WENDKOS

RHEUMATIC FEVER

Bywaters, E. G. L., and Thomas, G. T.: Prevention of Rheumatic Fever Recurrences. Brit. M. J. **2**: 350 (Aug. 9), 1958.

Two comparable groups of patients with rheumatic fever were followed for 5 years. One group of 96, admitted in 1949 to 1950, were given no prophylaxis. The other group of 88 patients, admitted in 1951 to 1952, were given 1 Gm. of sulfonamide daily. The period of follow-up study in the 2 groups overlapped by 2 to 4 years. The mean incidence of recurrences per patient-year was 5.6 per cent in the unprotected and 1.2 per cent in the protected group. There was only small variation from year to year in each group and no tendency for the recurrence rate to decrease with time. Toxic reactions to the sulfonamide were minimal and none was serious. It was pointed out that the recurrence rate in America for the unprotected group was far higher (18 to 25 per cent) than that in Britain. This may, in part, explain the fact that prophylaxis of rheumatic fever was taken up less enthusiastically in Britain than in the United States.

KRAUSE

VALVULAR HEART DISEASE

McCampbell, S. R.: Direct Atrial Pressure Tracings and the Degree of Mitral Obstruction. Brit. Heart J. **20**: 341 (July), 1958.

An analysis of the rate of fall of the diastolic portion of the left atrial tracing obtained before and after mitral valvotomy as suggested by Owen and Wood for pulmonary wedge tracings failed to determine the degree of obstruction at the mitral valve or to differentiate the presence or absence of mitral regurgitation.

SOLOFF

Heath, D., Edwards, J. E., and Smith, L. A.: The Rheologic Significance of Medial Necrosis and Dissecting Aneurysm of the Ascending Aorta in Association with Calcific Aortic Stenosis. Proc. Staff Meet., Mayo Clin. **33**: 228 (April 30), 1958.

The authors contend that when dissection occurs in the ascending artery just distal to a stenotic aortic valve, it is due to the hemodynamic effects of the stenosis. Repeated impacts on the vessels over a long period of time produce structural fatigue in an elastic artery with distention of its wall. These hemodynamic effects are due to changes in the velocity of blood flow, the development of lateral pressure, and eddies of alternating high and low pressures. In the case studied, the whole length of the aorta and pulmonary artery was examined for medial necrosis and this pathology was confined to the ascending aorta, where poststenotic dilatation was present. The authors state that medial necrosis can also occur in arteries remote from a stenotic valve in which event other factors besides hemodynamics must be considered abnormal. This, for example, can be found in the congenital form of aortic medial necrosis such as occurs in Marfan's syndrome.

KRAUSE

Verstraeten, J. M., Van Der Straeten, M., Verstraeten, J., and Pannier, R.: Pulmonary Elasticity in Mitral Stenosis. Acta cardiol. **13**: 262, 1958.

In 44 patients with mitral stenosis the transpulmonary pressure was recorded using a differential manometer, 1 side of which was connected with an intraesophageal balloon, while the other side was connected with the oral cavity; a spirometer recorded the pulmonary volume in the same tracing; a stopcock was used to interrupt the respiration at every displacement of 500 ml. of air. Data on pulmonary circulation, obtained by right heart catheterization, and on the ventilatory function were presented, with the calculated elastance and with clinical information for

each patient. It was found that the elastance increased in proportion to the severity of the mitral disease. Some relation was found between the elastance and the pulmonary arteriolar resistance. Changes in vital capacity, in the index of Tiffeneau, and in residual air were not important factors of changes in elastance. When the pulmonary capillary pressure was increased and fluid accumulated in the septa and in the alveoli, the elastance was also greatly increased. In patients undergoing mitral commissurotomy, it was found that the elastance was greatly increased in those patients in whom the biopsy of the lung showed interstitial fibrosis.

CALABRESI

Laake, H.: Rheumatic Tricuspid Stenosis. Acta med. scandinav. **161**: 109, 1958.

The diagnostic features of tricuspid stenosis are reviewed. A recording of the venous pulse in the neck was regarded as an important diagnostic aid. In the phlebogram of a patient with tricuspid stenosis and sinus rhythm there was a characteristically high a wave but if there were atrial fibrillation the a wave vanished. As the fall of pressure in the right atrium in tricuspid stenosis occurred gradually, there was no marked Y wave in atrial fibrillation in contrast to the findings in constrictive and exudative pericarditis. When there was coexistent mitral stenosis, the auscultatory findings in tricuspid stenosis could be difficult to assess. It was of value in the differential diagnosis between these 2 lesions to observe whether the diastolic murmur increased in intensity when the breath was held after a deep inspiration. When the negative intrathoracic pressure increased with inspiration the rate of flow of blood increased in the venae cavae and the murmur became higher pitched in tricuspid stenosis, whereas the opposite was true in mitral stenosis. It was characteristic of the murmur of tricuspid stenosis that it was accentuated with the patient on his right side. In a 10-year period, 54 patients with rheumatic heart disease were examined at autopsy and showed an incidence of tricuspid stenosis of 20.4 per cent. About one fourth of these had high grade stenosis, yet the correct diagnosis was made ante mortem in only 1 patient. This points up the fact that tricuspid stenosis is frequently not diagnosed ante mortem. An accurate clinical diagnosis of tricuspid stenosis assumes increasing importance in view of the operative treatment of rheumatic heart disease. The indications for mitral valvulotomy depend partly on whether there is co-existent tricuspid stenosis. Moreover, tricuspid stenosis itself is amenable to surgical treatment.

BROTHERS

VASCULAR DISEASE

Bruckner, W. J.: Significance of the Superior Vena Caval Syndrome. Arch. Int. Med. **102**: 88 (July), 1958.

The significance of the superior vena caval syndrome was reviewed on the basis of a series of 23 patients observed between 1947 and 1957. The symptoms and signs of the syndrome fell into 2 main categories: those of the primary disease and those due to venous obstruction itself. When compared with similar data collected before 1945, it was found that the incidence of primary thoracic tumor rose from 33 per cent to 38 per cent. Obstruction of the superior vena cava when caused by a benign lesion was compatible with long life; when caused by malignant disease, the outlook was extremely poor. When the diagnosis was suspected the adjuvant diagnostic measures of venous pressures, infrared photography, and contrast medium venography were recommended. The presence of the superior vena caval syndrome for longer than 6 months usually indicated that the lesion was benign and often could be relieved by surgery.

KRAUSE

Schoop, W., and Rau, G.: On the Cause of Arterial Changes in Arteriovenous Fistulas. Ztschr. Kreislaufforsch. **47**: 503 (June), 1958.

In 5 of 10 dogs with surgical anastomosis between the femoral artery and vein, repeated small injections of methylene blue caused less intense coloration of the arterial intima above the anastomosis than of the corresponding artery on the other side. This was attributed to a shorter time of contact between the dye and the intima due to increased blood velocity near the fistula. The ectasias in the artery leading to an arteriovenous fistula which are often found in human patients with such fistulas are attributed to deficient nutrition of the intima which is said to result from a decreased time of contact between blood and intima.

LEPESCHKIN

BOOK REVIEWS

Heart Disease and Pregnancy. Physiology and Management. C. Sidney Burwell and James Metcalfe. Boston, Little, Brown and Company, 1958, 338 pages, 44 figures. $10.00

This volume is an authoritative statement of our knowledge of the physiologic changes of pregnancy, the effects of the various types of heart disease, and the diagnosis and detailed treatment of these cardiac disorders. This treatise is an eminent successor to Hamilton and Thomson's study, at the Boston Lying-In-Hospital, of 850 pregnant women with heart disease published in 1941.

The authors state that if disease during pregnancy is to be well managed, the physiologic changes of pregnancy must first be known. Successive chapters deal with maternal adjustments to pregnancy, the organization of the cardiac clinic for proper management of their patients, the diagnostic criteria of heart disease in pregnancy, the prognosis of heart disease in pregnant women, and the details of the medical management of the pregnant patient with heart disease.

The authors state, "With present-day medical management and close cooperation between the patient, the obstetrician and the internist, more than 97 per cent of all cardiac patients who are capable of achieving pregnancy can be expected to survive it. The cardiac who has functionally severe heart disease runs an appreciably greater than average risk during pregnancy; so does the cardiac who is over 35 years of age." . . . "There is no evidence to indicate that the life expectancy of the woman with heart disease is shortened by pregnancy once she survives the pregnancy itself."

The diagnosis and treatment of the manifestations of rheumatic fever and rheumatic heart disease, congenital heart disease, and other disorders of the heart in pregnancy are delineated with admirable insight and clarity. Coronary disease as it occurs in association with pregnancy is reviewed and a variety of even rarer disturbances in pregnant women, such as thyroid disease, syphilitic heart disease, beriberi heart disease, postpartal heart disease, and constrictive pericarditis are discussed.

This book is a superb example of painstaking analysis of the pathologic-physiologic changes occurring in pregnant cardiac women which then is utilized as the basis for accurate diagnosis and a detailed practical program of medical management.

The volume is embellished by delightful references garnered from a multitude of literary sources. This book undoubtedly will be acknowledged as the authoritative statement of the subject and is highly recommended for all physicians concerned with cardiac patients and pregnancy.

HERRMAN L. BLUMGART

Electrocardiography. Michael Bernreiter. Philadelphia, J. B. Lippincott Company, 1958, 134 pages, 92 figures. $5.00.

This text represents the material used by the author in teaching medical students, general practitioners, and internists the elementary knowledge of electrocardiography. The book consists of 134 pages that include only 28 pages of text. The remainder consists almost entirely of diagrams and illustrative electrocardiograms. The book contains only the barest outline of the most essential information and qualifies as a lucid, readily comprehensible compendium for medical students in their initial study of the subject. The diagrams and electrocardiographic illustrations are excellent.

HERRMAN L. BLUMGART

AMERICAN HEART ASSOCIATION, INC.

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VARIED PROGRAM PLANNED FOR AHA SCIENTIFIC SESSIONS

A program which will integrate the contributions of the basic sciences, clinical experiences and medical care problems in the field of cardiology is being planned for the Association's 32nd annual Scientific Sessions, to be held from Friday, October 23 through Sunday, October 25 at the Trade and Convention Center in Philadelphia.

The Association's Council on Clinical Cardiology has been charged with preparing six sessions of broad clinical interest. These will run concurrently with special scientific sessions and Council programs in which original investigative work will be presented.

JOINT AHA SCIENTIFIC SESSION WILL BE HELD WITH AMERICAN COLLEGE OF CARDIOLOGY

For the first time the American Heart Association's annual Scientific Sessions will include a joint session with the American College of Cardiology. The College, which will be holding its 8th Interim Meeting concurrently, will also conduct its popular fireside conferences to which Heart Association members are invited.

ABSTRACTS OF PAPERS DUE JUNE 12 FOR SCIENTIFIC SESSIONS

June 12 is the deadline for submitting *abstracts of papers* to be presented at the 32nd annual Scientific Sessions of the American Heart Association, scheduled for October 23-25 in Philadelphia. Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and should contain a brief digest of the results obtained and the conclusions reached.

Official forms for submitting *abstracts of papers* and applications for *scientific exhibit* space, which also must be returned by June 12, may be obtained from Dr. F. J. Lewy, Assistant Medical Director, American Heart Association. Space for *industrial exhibits* may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, N. Y.

MEDICAL SOCIETIES ENDORSE HEART ASSOCIATION PROGRAM

Resolutions endorsing the programs of the American Heart Association and other major voluntary health agencies and expressing commendation for their contributions to medical research and the nation's health were voted recently by the American College of Surgeons and the Association of American Medical Colleges. In addition, the American Medical Association reiterated its position in support of the programs and independent fund raising policies of the AHA and other national health agencies.

The Board of Regents of the American College of Surgeons in December unanimously adopted a statement commending the AHA and others "for their substantial and intelligent contributions to health and to medical research." In February, the Executive Council of the Association of American Medical

Colleges resolved to "express its appreciation to the major voluntary health agencies for the invaluable contributions they are making, particularly toward the support of basic research, fellowships, scholarships and long-term research personnel support."

The AMA's House of Delegates, meeting in December, reaffirmed the resolutions of June, 1958, expressing the medical profession's confidence in the programs of the AHA and other agencies. Clauses were added stating that the AMA "neither approves nor disapproves of the inclusion of voluntary health agencies in United Fund drives," and calling for a top-level conference of the interested parties to discuss these problems.

LATEST VOLUME AVAILABLE ON HYPERTENSION PROCEEDINGS

Volume 7 of the proceedings of the Association's Council on High Blood Pressure is now available through local Heart Associations or through the American Heart Association at $2.50 a copy. The volume is based on the Council's Annual Meeting in November, 1958. In addition to the scientific and lay presentations given at the meeting, the volume includes discussions on hypertension by leading specialists in the field.

In addition, four volumes of the Council's proceedings, covering the years 1953 and 1955-57 respectively, may be obtained at a combined price of $6.00 from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

AHA RESEARCH COMMITTEE NAMES NEW CHAIRMAN

The Research Committee of the American Heart Association has elected Charles H. Rammelkamp, Jr., M.D., of Cleveland, as Chairman for the year 1959-60.

NEW ISSUE OF HEART BULLETIN CONTAINS AHA-INVITED PAPERS

The May-June issue of *The Heart Bulletin* consists of papers invited by Associate Medical Editors appointed by the American Heart Association. The Association sponsors the publication in cooperation with the National Heart Institute and the American Academy of General Practice.

Included are articles on *The Artificial Kidney*, by George E. Schreiner, M.D.; *The Coronary Collateral Circulation*, by Richard W. Eckstein, M.D.; *Aberrant Ventricular Conduction and its Clinical Significance*, by Alfred Pick, M.D.; *Essential Hypertension: Rationale for Early Treatment*, by Edward D. Freis, M.D.; and *The Electrocardiogram in Atrial Septal Defect*, by S. Gilbert Blount, M.D., Ray Prior, M.D., and George Woodwark, M.D.

The journal, with its concise and practical approach to the problems of every-day practice, is of particular value to the practicing physician in cardiovascular disease.

ABSTRACTS DUE JUNE 12 FOR ARTERIOSCLEROSIS COUNCIL MEETING NOVEMBER 8-9

June 12, 1959 has been set as the deadline for submitting abstracts of papers to be presented at the meeting of the Association's Council on Arteriosclerosis, to be held in Chicago's Hotel Knickerbocker on Sunday and Monday, November 8-9. Abstracts, not to exceed 250 words, should be sent in quadruplicate to Aaron Kellner, M.D., Program Chairman, New York Hospital, 525 East 68th Street, New York 21, N. Y.

The new Council, which was the American Society for the Study of Arteriosclerosis before its recent merger with the AHA, will also hold a scientific session and a symposium as part of the Heart Association's 32nd annual Scientific Sessions for which abstracts of papers to be presented also are due on June 12.

NATIONAL ORGANIZATIONS SPONSOR CV TRAINING PROGRAM

A postgraduate Cardiovascular Research and Training Program, jointly sponsored by the AHA and the National Heart Institute, will be conducted beginning July 1 in the Departments of Physiology and Pharmacology

at the Medical College of Georgia, Augusta. Participants will receive a stipend of $3,800 plus $350 for each dependent and certain expenses. Appointments are made on a one-year basis. Requests for application forms and inquiries may be made to the program directors, W. F. Hamilton, M.D., or R. P. Ahlquist, M.D., at the Medical College of Georgia.

MEDICAL TEACHING INSTITUTE

A second Summer Institute on Medical Teaching, presented by The University of Buffalo and The Association of American Medical Colleges, will be held from June 9-18 at The University of Buffalo. The first Institute, held in June last year, provided an unusual opportunity for 25 medical teachers representing 21 medical schools in the U. S. and Canada to study the complex problems of medical education under the stimulus and guidance of professional medical educators. Courses are free. A modest charge for lodgings and meals will be made by the University. Registrations may be made through Dr. George E. Miller, University of Buffalo School of Medicine, Buffalo 14, N. Y.

MEETINGS CALENDAR

May 26-29: American College of Cardiology, Philadelphia. Philip Reichert, 480 Park Avenue, New York 22, N. Y.

June 3-7: American College of Chest Physicians, Atlantic City. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 5-7: World Conference on Angiology, Atlantic City. Alfred Halpern, 11 Hampton Court, Great Neck, N. Y.

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

August 10-13: National Medical Association, Detroit, John T. Givens, 1108 Church Street, Norfolk, Va.

September 13-17: International College of Surgeons, U.S. Section, Chicago. Ross T. McIntire, 1516 Lake Shore Drive, Chicago 10, Ill.

September 22-25: American Roentgen Ray Society, Cincinnati. C. A. Good, 200 First Street, S.W., Rochester, Minn.

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, New York Hospital, 525 East 68th St., New York 21, N. Y.

ABROAD

June 24-27: 2nd International Conference on Medical Electronics, Paris, France, F. S. Brackett, National Institutes of Health, Bethesda 14, Md.

July 23-30: International Congress of Radiology. Munich, Germany. H. V. Braunbehrens, Ziemssenstr. 1, Munich 15, Germany.

July 27-30: Shaio Foundation Symposium on Cardiovascular Disease, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

September 18-20: International Cardiovascular Society, Munich, Germany. H. Haimovici, 715 Park Avenue, New York 21, N. Y.

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